EARLY TREATMENT OF STOVE-IN CHEST *

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A " stove-in chest " results from multiple rib fractures or from disruption of the costosternal cartilages; it is often complicated by other injuries, but its peculiar feature is paradoxical movement of the chest wall at the site of the fractures.

Paradoxical movement causes asymmetrical expansion and contraction of the thoracic cage; and this, in its turn, produces inadequate absorption of oxygen and elimination of carbon dioxide from the alveoli. These patients die from " respiratory failure " and not because a few bones have been broken. The purpose of this paper is to underline the fact that some who now die can be saved by simple treatments.

The perfection of fast touring cars and the construction of modern motorways have made these injuries common; but few surgeons are, as yet, experienced in the emergency treatments that may be vital. The victim is hurried away to the nearest hospital where he dies or survives almost irrespective of the things that may be done for the chest injury. A thoracic surgeon seldom sees the patient unless he survives for at least 48 hours; and so it behoves those responsible for the reception of accident cases to acquaint themselves with measures that are easy and effective.

Nature of the Injury

This type of chest injury occurs when the hoops composed of vertebral column, ribs, cartilages, and sternum are suddenly compressed. The direction of the forces that fracture the ribs is often an outward burst at the weakest parts of the hoops—as opposed to the local inward thrust of direct violence. Paradoxical movement can be recognised by looking at the chest wall as the patient breathes or, if this is not practicable, by palpation.

The critical extent of such an injury varies from patient to patient; the young tolerate more than the aged, and every moment the patient survives is time gained in his favour. If an injured person reaches a hospital alive respiratory failure should still be reversible; but minutes count.

An acquaintance with the management of thoraco-abdominal injuries sustained in war is not an adequate background for this work. The complications of stove-in chest are different. The importance of peritonitis and intra-abdominal hæmorrhage is eclipsed by concomitant head injuries and fractures of the long bones, vertebræ, and pelvis, and by complicating factors in the chest itself, as well as distension of the stomach and ileus.

Patients with multiple injuries, including " a stove-in chest ", often die without obvious cause. Hæmorrhage has been stemmed, transfusions have been given to combat shock, and ample morphine has relieved the sharp edge of the pain. The sedated patient lies quietly in bed and his shallow paradoxical respiratory movements escape critical notice. But death steps in suddenly, peacefully, naturally—and unnecessarily.

The accurate assessment of everything that contributes to this outcome is difficult; but, considering chest-wall injuries alone, the following points are relevant.

Paradoxical movement of the chest wall, uncomplicated by any serious intrathoracic injury, can be fatal. It was the principal cause of death in the early days of thoracoplasty. The harm it does is comparable to that of open pneumothorax, but of lesser degree in most cases. The flail area is sucked in as the chest expands, and blown out during expiration. The result is that some of the air that should be exchanged by passing in and out of the lungs, is shunted from one side of the chest, or from one part of the lung, to another. In severe cases this movement of air displaces the mediastinum to and fro during respiration, and this used to be called " pendulum movement ". It was considered to be dangerous because it was said to hinder blood returning to the right atrium; it *is* dangerous because it produces asphyxia.

It has been shown by bronchospirometry that a single, simple, rib fracture causes, reflexly, a measurable reduction of gas exchange in the lungs. This is due to a partial shut-down in the pulmonary vessels supplying the underlying lung. It is not of clinical importance if the patient's reserve of compensation is not seriously affected. But in severe injuries the resultant reflex pulmonary hypertension can eliminate gas exchange completely in all or part of a lung; and this happens even though the respiratory movements continue.

Pain upon respiration adds to the oxygen deficit by reducing the excursion of the chest wall and so by diminishing the volume of tidal air. Cough is suppressed because it hurts, and reflex spasm of the bronchial muscles contracts the lumen of the respiratory passages.

The patient has increasing difficulty in getting rid of bronchial and alveolar exudates, and the development of a " wet lung " is Nature's last cry.

Why secretions first accumulate in the bronchial tree is not clear. But it is certain that in the early hours after serious accident pulmonary œdema occurs; and this has been explained in several ways. Possibly the shut-down in the pulmonary vessels underlying an injured chest wall could cause anoxia and œdema of the affected alveoli. Alternatively the sudden diversion of a large proportion of the cardiac output might initiate hyperkinetic œdema in the sound lung. Cardiac failure and cerebral injuries may also play a part, and over-transfusion is a risk. Be these things as they may, the casualty surgeon must know that pulmonary œdema and retained bronchial secretions can kill within an hour of an accident, even though the lung itself has not been directly wounded. Moreover, the presence of bloodstained, watery expectoration is not necessarily due to a lung wound.

If a patient survives the initial risks of early pulmonary œdema, the retained secretions may become infected during convalescence and " bronchopneumonia " sets in. This should be preventable.

In addition to ventilatory difficulties the position is frequently aggravated by a lung wound, by intrapulmonary or intrapleural hæmorrhage or pneumothorax, by hernia if the diaphragm has been ruptured, or by acute dilatation of the stomach. Any, or all, of these can make breathing impossible.

* An address to the Society of Thoracic Surgeons of Great Britain and Ireland, Newcastle upon Tyne, November, 1959.

A major chest injury causes temporary restriction of the diaphragmatic excursions on the affected side. The dome of the diaphragm is always high.

A patient who has a " stove-in chest " and who reaches hospital alive is living on his pulmonary reserve. He now faces the additional hazard of being given morphine or other respiratory depressants.

The harmful effects of anoxia are cumulative and ultimately become irreversible.

Treatment

In the care of a patient with multiple injuries including a " stove-in chest ", attention cannot be confined to the chest injury; but in the first few hours treatment of this injury takes precedence over everything except primary hæmorrhage.

As a whole such treatment falls into three periods during which the aims are different. Immediately after the accident, and during the next 48 hours, the object is to correct inadequacies in the act of respiration. In those who survive, pulmonary infections must be forestalled, and total expansion of the lung on the affected side achieved and maintained. During convalescence normal movements of the chest wall and diaphragm must be regained.

The advice that follows concerns the emergency treatment only.

When a patient who has a " stove-in chest " and respiratory difficulty is admitted, give an anæsthetic, pass a cuffed intratracheal tube, and start controlled respiration. The anæsthetic is necessary to allow respiration to be controlled—and it is the latter that is important, not the former. Respiratory efforts by the patient can be abolished by producing alkalotic apnœa, by giving paralysing drugs, or using a combination of both. Intubation and controlled respiration saves life and has the additional advantage of enabling secretions to be sucked out of the air passages as often as they accumulate.

Experience in the treatment of recently wounded people during the late war, and particularly with young and otherwise healthy adults, showed that the critical state in which they were admitted to hospital was often due to inefficient respiration. As soon as the anæsthetist took over control of the act of breathing the clinical state improved, and, if the surgeon could then remedy the anatomical defects, so that spontaneous respiration could be resumed, the " come-back " was rapid and simple.

Once the patient has been anæsthetised in the out-patient department, the other injuries can be examined and a plan of campaign adopted. This is the moment to decide whether early operation of any type is necessary or not.

As far as the chest wall is concerned, determine the extent and position of the unstable areas, and examine the patient to discover other complications. If the anæsthetist, giving controlled respiration, cannot achieve easy movements on the affected side, the assumption should be that there is an intrathoracic complication. The usual reason why the affected lung cannot be inflated easily is that it is artificially restricted by pneumothorax, tension pneumothorax, blood in the pleural cavity, gastric dilatation, or diaphragmatic hernia.

It is not easy to be certain about any of these things clinically, and it may not be safe at this time to sit the patient up for an X-ray of the chest (a film taken in the recumbent position is confusing); but the following details may help. Observe the position of the apex beat, and remember that if breath sounds can be heard anteriorly, in the recumbent patient, an important pneumothorax is not present. Hæmothorax is particularly difficult to diagnose because, at this stage, the blood moves in the pleural cavity according to the position of the patient (" shifting dullness "). Thus, lying down, the lung floats forward on the blood in the paravertebral gutter and breath sounds are heard over the front of the chest; conversely when the patient sits forwards there are breath sounds at the back. For this reason a hæmothorax of several pints can be missed, unless the patient is examined, recumbent, with a flat stethoscope slipped in between the chest and the bed. The only way of diagnosing acute dilation of the stomach or diaphragmatic hernia at this stage is by an appropriate X-ray.

If the patient has, in addition to a stove-in chest, a hæmothorax, put an intercostal catheter into one or both pleural cavities and connect these to water-seal drainage bottles. The usual causes of traumatic hæmothorax are bleeding from the chest wall and, more rarely, from the lung; but in these days of rapid deceleration accidents rupture of the intima and media of the aorta is not uncommon. In such cases a false aortic aneurysm develops with oozing into the pleural cavity; they may live for as long as two months before the aneurysm bursts. If there is pneumothorax or tension pneumothorax, insert a small polyethylene tube, using a hydrocœle trocar, into the top of the affected pleural cavity through the second or third interspace anteriorly; connect the tube to a sealed drainage or suction apparatus. These emergency safety-valves can be maintained for two or three days without risk of intrathoracic suppuration; by this time definitive treatment will have been given and the tubes will have been replaced, or taken out. There is no merit in tubes that are blocked by clots in the lumen or by kinks in the dressings. If a pneumothorax or tension pneumothorax persists in spite of adequate continuous suction, rupture of a main bronchus should be suspected and, if present, treated by thoracotomy without delay.

Cardiac tamponade is a rare complication of stove-in chest, but if it be suspected the pericardium should be tapped by passing a long needle from the side of the xiphisternum upwards and backwards for a distance of about 10 cm. Blood that restricts the movements of the heart accumulates behind the ventricles and can be aspirated without difficulty. A misdirected tap is not dangerous because the needle approaches the least vascular part of the heart—that is, the apex.

The above measures may be necessary in the accident department. They are simple and, once completed, a proper assessment of the other injuries can be made without danger to the patient. The emergency time is over.

The surgeon must now decide how efficient respiration is to be maintained, and this decision is difficult. It will be obvious that if other treatments, such as traction for a fractured femur, are to be used, the management of the chest from now onwards must be unobtrusive and effective.

The first decision to take is whether the flail chest wall should be stabilised by local treatment; and several alternatives are available.

The first of these is to pad and strap the affected area. Do not do this, for these reasons. Strapping is easy to apply but difficult and painful to take off; the man who puts it on seldom has to take it off and, consequently, he does not shave the skin. It is a wasteful way of preventing paradox because, to be effective, the strapping must immobilise a much wider area than has been damaged. It may augment the respiratory inefficiency by fixing parts of

the chest wall that would otherwise move effectively. It makes X-rays difficult to interpret, and it hinders aspirations of the pleural cavity. It has no merit except ease of application.

There are a variety of minor operations that can be done under local anæsthesia and help some forms of paradox. The sternum can be elevated and held by traction applied to a cuphook screwed into the body of the bone and attached, over a pulley, to an appropriate weight. This can be effective.

The fractured ribs can be elevated and held by inserting several towel clips through the skin and around the mobile parts of the ribs, and applying traction in an outward direction.

Two or more Steinmann pins can be inserted under local anæsthesia, and through tenotome punctures in the skin, so that they cover the defect in a criss-cross fashion like boards nailed across a broken window. The pins rest upon the intact ribs and should be deep to the sheet muscles of the shoulder girdle.

These are temporary expedients, and are seldom used because they are not sufficiently good. But some surgeons are convinced of the necessity to stabilise the chest wall and they advocate open operation for the purpose.

To succeed in such a treatment it is necessary to elevate a wide flap of skin and muscles in the affected area and, having laid the fractures bare, to fix all the broken ribs—fore and aft—so that absolute stability is achieved. To do this one must use intramedullary pegs or wire the fragments in two planes. The operation is not difficult; but it takes time. Once completed there are no external splints or traction appliances to complicate treatment, and the intrathoracic injuries have been accurately assessed at the same time by opening the pleura and examining the thoracic viscera. An operation of this type eliminates paradoxical movement once and for all, and it prevents late persistent deformity of the thorax. It is true that, if it is not done, the late result of a stove-in chest may look like a lateral thoracoplasty and carry the attendant limitation of respiratory function in after-life. Many successes have been reported.

But, in general, these operations are seldom used, and for these reasons. They take time and add to the shock of the existing injuries. It requires mature judgment to balance the possible benefits against the trauma of the additional manipulations, and the problem of how to control bronchial secretions remains. Fortunately alternative treatments are available.

Whenever paradoxical respiration is so severe that it must be controlled, a tracheostomy should be done. Borrie says: " the time to do a tracheostomy is when considering whether or not it should be done ".

The operation is best done whilst the patient is under the anæsthetic given on admission, and whilst the anæsthetist's cuffed tube is in the trachea. It is simple and accurate to cut down upon a trachea splinted in this way, and to insert a plastic tracheostomy tube on which there is distensible balloon. The balloon need not be inflated, or used, until the result of tracheostomy has been assessed.

The benefits of tracheostomy are that, by diminishing dead space, the patient need not breathe so deeply to ventilate; secretions can be sucked out, oxygen can be given as occasion demands, and obstruction from paralysis of the tongue is eliminated. And mechanical respiration can be started if necessary.

Ingravescent surgical emphysema is a distressing complication of chest injuries. In general it signifies that the lung has been ruptured in one or more places, or it complicates an open pneumothorax that has sealed off; coughing then injects the air, trapped in the pleural space, into the subcutaneous tissues of the chest wall or into the mediastinum and the neck. A tracheostomy controls, prevents, and eliminates surgical emphysema.

It is an unexpected but commonly observed fact that by doing a tracheostomy, and nothing more, the problems of inefficient respiration are solved in many cases. This is particularly true in elderly or bronchitic subjects.

When repeated toilet of the air-passages, by catheter suction is used, *sterile* catheters must be available for the purpose. If this precaution is not taken the patient will probably be given staphylococcal pneumonia, or may acquire an equally intractable organism. This type of complication can determine the issue.

If tracheostomy by itself fails to control the harmful effects of paradoxical movement, or if other complications, such as coma due to an associated head injury, demand more definite measures to ensure efficient respiration, the balloon on the intratracheal tube can be inflated, and the patient connected to a breathing-machine. If this decision has been taken the outlook is serious but not by any means hopeless. There are few circumstances, excluding severe lung or vascular injuries, in which efficient respiration cannot be continued for as long as may be necessary. These patients can be kept alive. But prolonged controlled artificial respiration is not to be lightly pursued by all and sundry, and at this stage the patient should probably be transferred to a unit that specialises in this work. If necessary artificial respiration can be continued in the ambulance whilst the patient is transferred to a respiratory unit, using the hand bellows that are now available.

After tracheostomy, or other definitive treatments, steps must be taken to alleviate pain. The danger of giving morphine, or its derivatives, is stressed by almost everybody who has treated these patients. It depresses cough, encourages retention of bronchial secretions, and favours the development of septic pneumonia. The best alternative is to inject local anæsthesia into the vicinity of the fractures. A single injection may not be enough, but the effects often last longer than one expects. If chest-wall pain continues, a small polyethylene catheter can be introduced into the traumatised area and through this small but adequate amounts of local anæsthetic and antibiotic can be instilled as necessary.

Conclusions

The immediate procedures advocated in this paper and purporting to control the dangerous effects of " stove-in chest " are simple.

The battle that must be won during the first few hours, and the position that must be held for subsequent days or weeks, is against anoxia and carbon-dioxide retention.

Strapping the chest wall, morphine, and barbiturate sedatives are contraindicated. The use of " Drinker type " respirators is bad because they compress the flail chest wall.

The procedure, on admission to a hospital, that I recommend in cases of respiratory embarrassment due to " stove-in chest " is this:

1. Anæsthetise the patient straight away in order to achieve controlled respiration.
2. Examine the patient and assess the relative priorities of multiple injuries.
3. Eliminate the additional burdens of hæmothorax, pneumothorax, tamponade, dilatation of the stomach, or

diaphragmatic hernia, by appropriate catheterisation, sealed drainage, or suction.

4. Improve the efficiency and ease of respiration by tracheostomy if necessary.

5. Institute controlled respiration using a mechanical breathing machine in desperate cases.

6. Control pain by local injections of anæsthetic solution. Do not give morphine unless or until efficient respiration is assured.

If, after tracheostomy, it be decided that a mechanical breathing machine must be used, adequate apparatus and personnel must be available. A patient kept alive artificially in this way requires constant medical and nursing care, at least in the early days of treatment.

The high mortality associated with " stove-in chest " is due to cardiorespiratory failure, and notably to anoxia and carbon-dioxide retention.

BRETYLIUM TOSYLATE IN THE TREATMENT OF HYPERTENSION

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SUCCESSIVE advances in the treatment of high blood-pressures have been made possible by the steady output of new and improved drugs. Until recently all the really potent drugs acted by blocking the autonomic ganglia. Pressure reduction was invariably accompanied by partial paralysis of the parasympathetic system with consequent dry mouth, blurred vision, constipation, and impotence. In some patients episodes of paralytic ileus threatened life, particularly when renal function was impaired. Because of these difficulties only the most severely ill were selected for treatment. The severity of side-effects varied greatly from patient to patient, but only a minority were unable to tolerate the regime. All patients, however, had to endure inconvenience and even at times incapacity from the drugs and this made it difficult to achieve optimal pressure reduction in all. The elimination of these parasympathetic side-effects would clearly be a desirable contribution by improving the toleration of treatment.

The first lead towards a drug of this type was TM10 (Hey and Willey 1954), which had a selective paralytic action on the postganglionic adrenergic neurones but unfortunately also stimulated parasympathetic fibres—a property which made it useless therapeutically (Bain and Fielden 1957). Recently a much more promising drug, bretylium tosylate (' Darenthin '), has been described (Boura et al. 1959). This drug paralyses adrenergic neurones without significant effect on the parasympathetic system. These workers reported the results of treatment in 36 patients with hypertension; and in every patient except 1, who had a phæochromocytoma, pressure reduction was achieved. In 4 patients the treatment had to be stopped because of symptoms associated with postural hypotension. Side-effects were trivial, and the only one of importance was stuffiness of the nose. In view of this encouraging report we have employed bretylium in the treatment of severe hypertension, at first only in those suffering severely from side-effects of ganglion blockade and later in a number of new patients receiving treatment for the first time. The main difficulties encountered resulted from the variability of the degree of fall of blood-pressure, and studies of absorption were made to clarify this problem.

Patients and Methods

A total of 50 patients were given oral maintenance treatment with bretylium during the six-month period of this trial. 28 of them had previously been treated with ganglion-blocking drugs, usually pempidine or mecamylamine. Initially only those patients with very severe side-effects or poor control of blood-pressure were transferred from the ganglion-blocking drugs, but later some with less severe side-effects were switched to bretylium. All the patients had severe hypertension and 22 had hæmorrhages, exudates, or papillœdema in the retina when treatment had first been started. Other indications for treatment included: hypertension with chronic renal disease, hypertension in pregnancy, hypertensive heart-failure, and severe high pressure and symptoms.

All the patients were admitted to hospital for stabilisation on bretylium. 5 patients were first treated with intravenous doses of bretylium because acute reduction of the blood-pressure was required. Intravenous treatment was unsatisfactory, and subsequently all patients were treated with the 200 mg. oral tablets of bretylium tosylate. The usual starting dose was 600 mg. daily given as one tablet after breakfast, lunch, and supper. The dose was increased daily by 300 to 600 mg. until a satisfactory fall in the pressure was achieved. In hospital the blood-pressure was recorded with the patient lying down and standing up at least four times daily. Patients with malignant hypertension or left ventricular failure were nursed propped up on pillows and with the bed head raised on 12 in. blocks. Less severely ill patients were encouraged to sit in chairs or walk about the ward as much as possible. Out-patients were seen at short intervals in a special clinic for hypertensive patients.

Absorption Studies

Bretylium labelled with ^{14}C was available as a sterile solution containing 5 μC of radioactivity with 30 mg. of bretylium iodide for intravenous use and 5 μC with 200 mg. bretylium tosylate for oral use. The maximum dose approved for use in patients was 5 μC because of the long half life of ^{14}C. As the permissible dose was small measurements had to be confined to the excretion in the urine after oral and intravenous doses. The twenty-four-hour excretion after an oral dose was measured in 10 fasting patients. 6 other patients were studied on two separate occasions to compare the eight-hour excretion. The twenty-four-hour excretion of bretylium after intravenous doses was measured in 6 patients, 4 with normal renal function and 2 with blood-urea values of about 120 mg. per 100 ml.

^{14}C was counted in a liquid scintillation counter (Jones et al. in press). 1 ml. urine samples were added to the toluene-alcohol-scintillator mixture and counted directly. Errors from quenching due to other constituents of urine were avoided by counting the standards in the presence of equal quantities of the same urine samples.

Results

ABSORPTION AND EXCRETION STUDIES

Intravenous Doses

The total excretion in twenty-four hours following an intravenous dose is tabulated in table I. The recovery in

TABLE I—TWENTY-FOUR-HOUR EXCRETION AFTER INTRAVENOUS ^{14}C BRETYLIUM DOSES

Case no.	Blood-urea (mg. per 100 ml.)	24-hr. excretion (%)
1	37	65
2	40	60
3	36	83
4	32	74
5	115	23
6	120	31

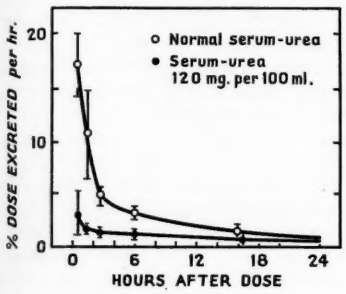

Fig. 1

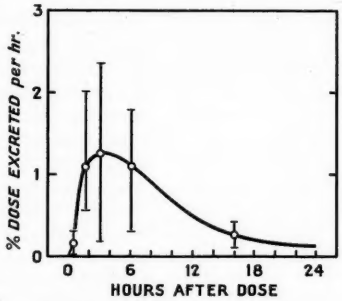

Fig. 2

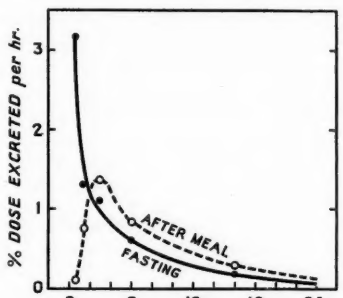

Fig. 3

Fig. 1—Fractional excretion of ^{14}C bretylium for 24 hours following intravenous administration in 4 hypertensive patients with a normal blood-urea and 2 with a blood-urea of about 120 mg. per 100 ml. Open circles indicate mean excretion in patients with a normal blood-urea and closed circles the uræmic patients. The vertical lines show the range.

Fig. 2—Fractional excretion of ^{14}C bretylium in 7 patients given oral doses while fasting. The circles indicate the mean excretion per hour at the midpoint of each collection period, and the vertical lines show the range.

Fig. 3—Fractional excretion of ^{14}C bretylium in a patient who showed a rapid initial excretion after a fasting dose and was given a second dose after a meal.

the 4 patients with normal blood-urea ranged from 65 to 83% with a mean of 71%. The 2 patients with a raised blood-urea excreted only 23% and 30%. The fractional excretions of these 2 patients are compared with those of the other 4 patients in fig. 1.

Oral Doses

10 patients were given 5 μC oral doses of bretylium while fasting and the excretion was measured over the following twenty-four hours. The total excretion ranged from 5·1% to 18·3% with a mean of 12·9% (table II). The lowest excretion was from a patient with a blood-urea of 74 mg. per 100 ml.; another with a blood-urea of 79 mg. per 100 ml. excreted 14·6% of the dose in twenty-four hours. The renal functions of the other patients may have been slightly impaired but the blood-urea concentrations were within the normal range. The fractional excretion was measured in 8 patients, and in 7 it showed a similar pattern (fig. 2). Excretion was maximal between the second and eighth hours after the dose, but in 1 patient there was much more rapid initial excretion although the twenty-four-hour excretion was only 11·6%. This patient was restudied with the dose given after a meal, and the excretion then conformed to the more usual pattern (fig. 3).

Paired absorption studies were made in 6 patients. The eight-hour excretion was compared when the dose was given fasting and again after a meal. Absorption was greater when the dose was taken fasting (table III).

These studies have proved the incomplete and probably irregular alimentary absorption that has a considerable bearing on the problems of treatment.

TABLE II—TWENTY-FOUR-HOUR URINARY EXCRETION AFTER ORAL ^{14}C BRETYLIUM DOSES

Case no.	24-hr. excretion (%)	Blood-urea (mg. per 100 ml.)
7	17·9	44
8	6·7	34
9	11·6	30
10	18·2	44
11	14·5	79
12	5·1	74
13	10·4	30
14	17·0	32
15	12·8	39
16	15·2	40
—	Mean 12·9	—

TREATMENT OF HYPERTENSIVE PATIENTS

Intravenous Doses

4 patients with left ventricular failure and 1 with acute nephritis and hypertensive encephalopathy were treated with intravenous doses of bretylium iodide ranging from 200 to 600 mg. 1 patient with left ventricular failure had a satisfactory fall in blood-pressure, but the other 4 patients did not. All the patients were nauseated immediately after the injection and 4 of them vomited. This happened despite dilution of the dose 10:1 in 5% dextrose before injection.

TABLE III—EIGHT-HOUR URINARY EXCRETION AFTER ^{14}C BRETYLIUM ON TWO SEPARATE OCCASIONS

Case no.	Dose after a meal (8-hr. excretion) (%)	Fasting dose (8-hr. excretion) (%)
17	6·9	9·1
18	13·4	21·4
19	12·9	18·5
20	0·1	8·4
21	9·6	16·0
22	4·1	6·7

Oral Maintenance Treatment

50 patients were started on oral maintenance treatment with bretylium tosylate. The final dose which controlled the pressure ranged from 200 mg. to 3600 mg. daily with a mean of 1800 mg. In 6 patients blood-pressure could not be controlled even with the largest doses. It is difficult to analyse concisely all the results obtained in this large group of patients. To facilitate presentation the patients have been divided broadly into those with a satisfactory result and those who were unsatisfactory.

Patients referred to as *satisfactory* had at least a 20 mm. Hg fall in the diastolic blood-pressure on standing or a standing pressure of 160/90 mm. Hg or lower.

Patients listed as *unsatisfactory* had either little reduction of blood-pressure or were intolerant of the drug in some way.

These data are shown in table IV with the hypertension divided into different groups. A striking feature is the poor results obtained in the patients with malignant hypertension; only 3 out of 11 were satisfactory. However, the patients without retinitis or papillœdema showed a much more favourable response; 21 out of 28 were satisfactory. The arbitrary division into satisfactory and unsatisfactory conceals all gradations from excellent to

TABLE IV—RESULTS OF TREATMENT WITH ORAL BRETYLIUM

Indication for treatment	Satisfactory	Unsatisfactory	Total
Malignant hypertension (papillœdema)	3	8	11
Grade-3 hypertension (retinal hæm. or exudate)	6	5	11
Hypertension complicating chronic nephritis	7	2	9
Other severe hypertension with symptoms	11	3	14
Left ventricular failure	2	0	2
Hypertension in pregnancy	1	2	3
All causes	30	20	50

disastrous, but it does convey the overall picture without much distortion. Many of the patients who had previously been treated with ganglion-blocking drugs were deeply grateful for the freedom from constipation, and for some the change was so dramatic that they were almost lyrical in their praise of bretylium. A number of young hypertensives treated from the beginning with bretylium showed an excellent response and the drug seemed to interfere very little with their daily life.

Causes of Treatment Failure

The high proportion of unsatisfactory responses in the malignant group makes it worth while to examine them in more detail. The 3 responses regarded as satisfactory included the only 2 malignant hypertensives treated with bretylium from the beginning. Both these patients have shown regression of hæmorrhages, exudates, and papillœdema with treatment. The 3rd had rather less satisfactory control of blood-pressure, but he developed a subacute dissecting aneurysm of the aorta and died of uræmia. There is no reason to incriminate this particular drug in this disaster. The 8 patients with malignant hypertension whose response was unsatisfactory had all been treated previously with ganglion-blocking drugs and had proved difficult to manage. 5 of them were not controlled by large doses of bretylium (2400–3600 mg. daily) with added chlorothiazide and had to be transferred to other drugs; 2 of them subsequently died of uræmia and the other 3 are at present being treated with pempidine. 2 of these patients initially responded to moderate doses of bretylium, and the 3rd, who was having 3600 mg. of bretylium daily, had one severe fall of pressure although it remained very high on numerous other occasions. Of the remaining 3 patients 1 is being treated with a combination of bretylium and pempidine and the other 2 are inadequately controlled by bretylium at present but have not reached maximum doses.

Among the less severe hypertensive patients there were fewer failures, and most of these were caused by fluctuations in the pressure-lowering action. 2 patients had minor strokes and 1 a myocardial infarction during periods of low pressure; fortunately all 3 recovered completely. Abrupt falls of pressure are a serious hazard in patients with vascular disease of the brain or myocardium, and they seem to occur more commonly with bretylium than with the more regularly absorbed pempidine or mecamylamine. Several patients who had been accustomed to ganglion-blocking drugs complained of a feeling of insecurity with bretylium because they could not predict when postural hypotension might occur. For this reason 3 of them asked to return to ganglion-blocking drugs even though in other respects they preferred bretylium.

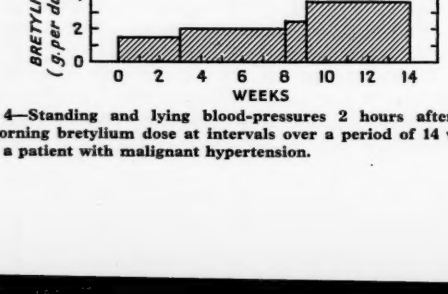

Fig. 4—Standing and lying blood-pressures 2 hours after the morning bretylium dose at intervals over a period of 14 weeks in a patient with malignant hypertension.

Tolerance

Minor degrees of tolerance may have passed unnoticed while the dose was slowly increased to gain control of the blood-pressure. Over longer periods a number of patients required increasing doses to secure the same reduction of blood-pressure. 1 such patient was well controlled with 1500 mg. daily at the beginning, but over the succeeding three months required a progressive increase to 3600 mg. daily (fig. 4); when this dose proved ineffective the patient had to be transferred back to pempidine. Fortunately most patients have required only moderate increases, but the margin between present dosage and the maximum daily intake of, say, 18 tablets is small.

Side-effects

Many patients noticed mild nausea with oral bretylium, and 2 uræmic patients were troubled by both nausea and vomiting which ceased when the drug was stopped. Nasal stuffiness was frequently present but only 2 patients volunteered complaints about it. 2 patients complained of tightness of the skin around the nose and lower eyelids, and in 1 this was associated with severe nasal stuffiness. 4 patients noticed tenderness of the parotid gland at the angle of the jaw, especially when eating. 3 patients noticed visual impairment; in 2 of them objects close up seemed blurred, perhaps owing to accommodation difficulty, and the other noticed undue brightness of vision at a time when the pupil was small—for which we have no explanation. 1 patient developed a fine papular erythematous rash which disappeared when bretylium was stopped. When broken tablets had to be given some patients complained about the very bitter taste. About two-thirds of the patients, however, were not subjectively troubled to any important extent.

Deaths

5 patients who had been treated with bretylium died during the period of this study. 2 died of uræmia, 1 of a dissecting aneurysm, 1 of cerebral hæmorrhage, and 1 of polyneuritis of the Guillain-Barré type.

Discussion

Our experience with bretylium suggests some general conclusions about its place in the treatment of severe hypertension. Bretylium is an effective drug which has a low incidence of serious side-effects. It is probably the drug of first choice for "benign" hypertensive patients without ischæmic vascular disease who are being treated for the first time. In patients with cerebral or myocardial ischæmia a fully-absorbed drug such as pempidine or mecamylamine is probably safer. Any potent hypotensive drug may, rarely, precipitate a stroke or myocardial infarction in patients with occlusive vascular disease, but the risk is greater with a drug such as bretylium which gives rise to occasional unpredictable severe falls of blood-

pressure. Some of the fluctuations in the hypotensive action of bretylium must be the result of variable absorption. This is to be expected with any drug which is poorly absorbed from the gut, because small changes in the proportion absorbed (say from 6 to 12%) may cause relatively large changes in the pharmacological effect. The results for the excretion of bretylium after oral and intravenous doses are comparable with the results obtained by Milne and Oleesky (1951) and Harington (1953) in studies with the quaternary-ammonium ganglion-blocking drug, hexamethonium. The only important difference is that the mean twenty-four-hour excretion of bretylium after oral doses is 12·9%, whereas for hexamethonium it is 5·4%. As the absorption of bretylium is appreciably greater than that of hexamethonium, fluctuations in absorption could be less dangerous. The patient who showed a very rapid initial absorption after a fasting oral dose of bretylium is of interest because this may account for sudden falls of pressure observed in some patients. The paired eight-hour excretion studies showed that the absorption after a fasting dose was always greater than after a meal. The slow excretion of bretylium after intravenous doses in patients with uræmia emphasises the need for care with these patients, who may accumulate the drug over several days and then become suddenly and persistently hypotensive. 1 such patient was faint on standing for five days after stopping oral bretylium.

Patients with severe hypertension, particularly malignant hypertension, required large doses of bretylium to control the blood-pressure. When bretylium proved ineffective in maximum doses the addition of chlorothiazide or strict sodium restriction caused a moderate increase in the hypotensive action. More than half (13 out of 22) of the severe hypertensives were not controlled by these measures and had to be transferred back to ganglion-blocking drugs. Some of these patients were at first controlled by bretylium but became unresponsive after weeks or months. Tolerance of this kind is a serious problem because the difference between the effective dose and the maximum dose is often small. There is a real need for a drug which retains the pharmacological specificity of bretylium but which has a greater activity per unit weight.

The overall results of treatment with bretylium in our series were less good than those recorded by Boura et al. (1959) and by Smirk and Hodge (1959). There are two possible explanations of this discrepancy. Our series contained a high proportion of very severe hypertensives and a number of patients who had responded poorly to large doses of ganglion-blocking drugs. These patients proved to be relatively insensitive to bretylium. The second possibility is that longer follow-up has revealed a larger number of patients in whom bretylium is becoming less effective.

In the present trial patients who had retinal hæmorrhages, exudates, or papillœdema fared badly when they were treated with bretylium. It is, therefore, inadvisable to switch such patients to bretylium if their blood-pressure is well controlled by other drugs. If patients with retinitis have side-effects which are so severe that pressure control has to be relaxed it may be useful to try them on bretylium. Patients without retinitis or papillœdema can be transferred without much difficulty, and less severe side-effects may make the change desirable.

Bretylium is a step forward along a difficult road. It allows control of blood-pressure in many patients without some of the miseries that accompanied ganglion blockade, but it is less reliable than pempidine or mecamylamine as a pressure-lowering agent. The reduction of blood-pressure is brought about by sympathetic paralysis and in consequence the management of the patient on bretylium is very similar to that of patients on ganglion-blocking drugs. Frequent follow-up and careful adjustment of the drug dose are essential if good results are to be sustained.

Summary and Conclusions

Bretylium tosylate facilitates the management of hypertensive patients on long-term oral treatment because of the low incidence of side-effects. The best results were obtained in hypertensive patients without retinal hæmorrhage, exudates, or papillœdema, and in this group 75% showed a satisfactory response. Only 41% of the patients with retinitis or papillœdema were satisfactorily managed. The malignant hypertensive patients who had been difficult to manage with pempidine or mecamylamine usually proved insensitive to oral bretylium in the doses used in this trial.

10 hypertensive patients given ^{14}C-labelled oral bretylium excreted a mean of 12·9% of the dose in twenty-four hours. 4 hypertensive patients given intravenous doses excreted a mean of 73% in twenty-four hours. Irregular and incomplete absorption after oral administration probably contributed to the variable falls of pressure in some patients. Such unpredictable falls of blood-pressure are dangerous in patients with occlusive vascular disease of the brain or heart.

We should like to thank Dr. David Long, of the Wellcome Foundation, for supplies of labelled bretylium.

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RENAL POLYCYTHÆMIA

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THE association of polycythæmia with renal carcinoma has now been reported in over 30 patients, and the subject has been reviewed by Damon et al. (1958) and Forssell (1958). The occurrence of polycythæmia with renal tumours other than carcinoma has been described in 2 cases (DeMarsh and Warmington 1955, Lawrence and Donald 1959). Where nephrectomy has been possible long remissions of the polycythæmia have occurred in some cases.

Recently there have been a few reports of polycythæmia with non-neoplastic renal lesions; polycystic kidneys

were present in 4 of these cases (Forssell 1958) and hydronephrosis in 3 (Cooper and Tuttle 1957, Gardner and Freymann 1958, Lawrence and Donald 1959). This combination is probably commoner than the few reports of it would suggest; thus Kurrle (1954) described as a case of Gaisböck's syndrome a patient in whom polycythæmia and hypertension were associated with polycystic kidneys. In 5 of these 8 cases the diagnosis of polycythæmia was established by measuring the total red-blood-cell volume indirectly by plasma-volume/hæmatocrit methods. In 1 case it was shown that the red-cell volume diminished after nephrectomy.

We report here 2 cases of polycythæmia associated with non-neoplastic renal disease. In both patients polycythæmia disappeared after nephrectomy.

The relationship between renal disease and excessive erythropoiesis acquires added significance in the light of experimental work implicating the kidney as one possible source of erythropoietin (Jacobson et al. 1957, Osnes 1958). In the 2 cases reported here plasma-erythropoietin levels were initially elevated and fell to normal after nephrectomy.

Methods

Red-cell volume was measured by the ^{51}Cr method (modified from Veall and Vetter 1958).

Plasma volume was determined with an Evans-blue dye technique.

Lean body mass.—For reasons discussed later red-cell volume was related to lean body mass (L.B.M.). The latter was calculated from the total body-water (T.B.W.) using the relationship $\frac{\text{T.B.W.}}{0{\cdot}73} = \text{L.B.M.}$ (Pace and Rathbun 1945). The volume of distribution of administered urea was considered to measure T.B.W. (McCance and Widdowson 1951). Three estimations of the urea space were made on each occasion (Prunty et al. 1959).

Iron metabolism.—Plasma-iron levels were measured by the method of Bothwell and Mallett (1955). Plasma-^{59}Fe half-clearance times ($T^1/_2$) were determined by standard procedures (Veall and Vetter 1958). The disappearance-rate constant is given by $\frac{\text{Log}_e\ 2}{T^1/_2}$. From these data may be calculated the *plasma-iron turnover*, which was expressed as mg. per 100 ml. blood per day (Bothwell et al. 1957).

Plasma erythropoietin activity was assayed by a technique which is to be described elsewhere (Payne 1960). Briefly this is a "four-point" bioassay using the reticulocytosis induced in rats by intraperitoneal injections of graded doses of the subject's plasma. In each group of assays the test plasma is compared with pooled normal plasma. Considerable experience with this technique has now been obtained, and the reproducibility and validity of its results are established.

Case-reports

Case 1.—A 57-year-old man was admitted to hospital in April, 1959, with left hemiplegia of sudden onset. During the previous two years he had experienced "bursting" feelings in the head, particularly on stooping. On examination the following findings were noted: left hemiplegia; blood-pressure 210/120 mm. Hg; normal optic fundi; auricular fibrillation; signs of mitral stenosis; no rise in jugular venous pressure; a large cystic mass palpable in the abdomen extending from the left loin to the suprapubic area.

The urine contained 60 mg. protein per 100 ml., a few leucocytes and red blood-cells, and was sterile. Electrocardiography confirmed auricular fibrillation; a chest X-ray showed a slightly enlarged heart shadow; blood-urea levels varied between 40 and 48 mg. per 100 ml.; plasma sodium, potassium, chloride, and bicarbonate levels were within normal limits on several occasions; creatinine clearance was 85 ml. per minute; intravenous pyelography showed a normal calyceal pattern in the right kidney but no excretion of dye by the left kidney, and retrograde pyelography revealed a very large left hydronephrosis.

The patient appeared plethoric, and was found to have a hæmoglobin of 21·8 g. per 100 ml., a packed-cell volume (P.C.V.) of 62%, a red-blood-cell count of 6,800,000 per c.mm., a white-blood-cell count of 9,900 per c.mm. with a normal differential cell-count, a platelet-count of 171,000 per c.mm., and an erythrocyte-sedimentation rate of 1 mm. in the first hour (Westergren); the highest values recorded are quoted.

Examination of the sternal marrow showed slight erythroid hyperplasia. The spleen was not palpable. The total body-weight was 72·0 kg., the urea space 42·8 litres, and the lean body mass 58·6 kg.

The diagnosis of polycythæmia was established by the finding of an increased red-cell volume (R.C.V.). Further investigations of the polycythæmia are described under "Results". Despite the absence of cyanosis the presence of the heart lesion made it important to exclude an anoxic cause of the polycythæmia; the arterial blood-oxygen saturation was normal (95%).

On June 8, 1959, left nephrectomy was performed. A huge thin-walled hydronephrotic sac containing about 6 litres of milky fluid was found; this fluid was sterile. No kidney tissue could be identified macroscopically, and histological examination of the sac wall showed fibrous tissue infiltrated by chronic inflammatory cells and containing a few renal tubular elements. At operation blood samples were obtained from the aorta, the left renal vein, and a peripheral arm vein at the same time. These samples were assayed for erythropoietin activity, and the results are discussed later.

Postoperatively the patient's recovery was uneventful. Subsequent changes in hæmoglobin and hæmatocrit levels are shown in fig. 1. The white-cell and platelet counts remained normal. Postoperative studies of red-cell volume, iron metabolism, and erythropoietin levels are described below.

Case 2.—This obese 55-year-old railwayman was found to have auricular fibrillation at a routine medical examination. When he was admitted to hospital no other signs of heart-disease were found, there was no evidence of cardiac failure, the blood-pressure averaged 160/90 mm. Hg, the heart was not enlarged radiographically, and electrocardiography showed only auricular fibrillation. He appeared to be euthyroid. An unsuccessful attempt was made to bring about reversion to normal cardiac rhythm with quinidine.

The patient had a plethoric complexion and was found to have a hæmoglobin of 18·8 g. per 100 ml., P.C.V. 57%, a platelet count of 185,000 per c.mm., a white-blood-cell count of 13,000 per c.mm. (neutrophils 80%, lymphocytes 16%, monocytes 4%); the highest values recorded are quoted. The spleen was not palpable. The diagnosis of polycythæmia was confirmed by the finding of an increased red-cell volume. Further studies of the polycythæmia are described below.

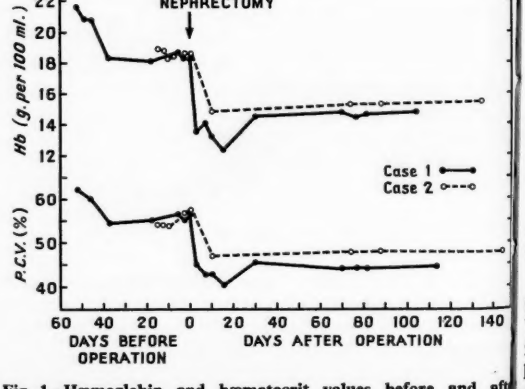

Fig. 1—Hæmoglobin and hæmatocrit values before and after operation.

TABLE I—RED-CELL VOLUME AND ^{59}Fe RESULTS BEFORE AND AFTER OPERATION

Case no.	Time	Red-cell volume (ml.)	Red-cell volume (ml. per kg. body-weight)	Plasma volume (ml. per kg.)	Plasma-iron (μg. per 100 ml.)	$T^1/_2$ ^{59}Fe (min.)	^{59}Fe-disappearance-rate constant ($hr.^{-1}$)	Plasma-iron turnover (mg. per 100 ml. blood per day)
1	2 weeks preop.	2805	39·0	45·6	91	54	0·77	0·80
	4 weeks postop.	2103	32·2	49·5	...	...	...	...
	11 weeks postop.	2165	30·5	48·8	102	75	0·55	0·75
2	2 weeks preop.	3317	33·2	32·8	75	28	1·49	1·20
	11 weeks postop.	2468	25·7	35·6	88	72	0·58	0·64
Normal values	..	..	..	..	70–180	70–140	0·33–0·69*	0·38–0·77†

* Bothwell et al. (1956). † Bothwell et al. (1957).

The total body-weight was 100 kg., the urea space 52·0 litres, and the lean body mass 71·3 kg.

To exclude a renal cause of the polycythæmia intravenous pyelography was performed. The left kidney appeared normal, but on the right side the upper calyceal group was much dilated, the upper pole of the kidney was enlarged, and a rounded indentation of the calyx was seen. The blood-urea was 25 mg. per 100 ml. and the creatinine clearance was 75 ml. per minute. The urine contained an occasional leucocyte but no protein and was repeatedly sterile; no tubercle bacilli were seen in it, and Löwenstein cultures were negative. The right kidney was explored surgically on May 2, 1959, and a large multilocular cyst was removed from the upper pole. Several smaller cysts were present in the remainder of the kidney, but this was left in situ as considerable normal tissue appeared to be present. Histological examination of the cyst showed the wall to be largely fibrous although lined in part by cuboidal epithelium. There was no evidence of malignant change.

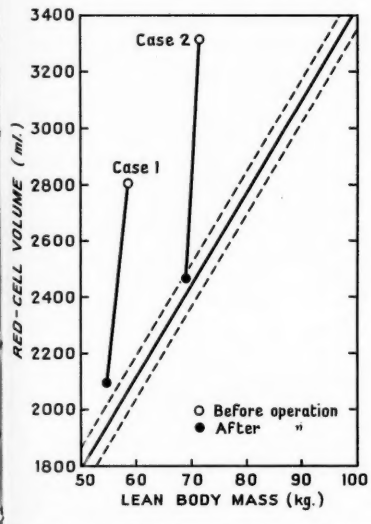

Fig. 2—Red-cell volumes before and after operation.
The solid regression line relating the normal mean red-cell volume to lean body mass is taken from the data of Muldowney (1957), ($y = 32{\cdot}74\,x + 155{\cdot}17$). The interrupted lines represent 95% confidence limits.

Postoperatively the patient has remained well for six months to date, although auricular fibrillation has persisted. Three months after operation the following findings were obtained: Hb 15·1 g. per 100 ml.; P.C.V. 48%; platelets 270,000 per c.mm.; white blood-cells 8900 per c.mm. The R.C.V. was now normal. Further studies are described below.

Results

Red-cell Volume, Hæmoglobin, and Hæmatocrit (see table I and figs. 1 and 2)

Before nephrectomy both patients had raised hæmoglobin concentrations: 21·8 g. and 18·8 g. per 100 ml. The highest hæmatocrit values were 62% in case 1 and 57% in case 2. After operation the hæmoglobin and hæmatocrit values returned to normal (fig. 1) and have remained so.

In case 1 the red-cell volume (R.C.V.) before operation was found to be 2805 ml., whereas the upper 95% confidence limit for normal R.C.V. predicted from the lean body mass was 2145 ml. Four weeks after nephrectomy the R.C.V. was 2103 ml. Owing to weight loss the predicted upper limit of normal at this time was 2014 ml.

In case 2 the R.C.V. before nephrectomy was 3317 ml., whereas the upper limit of normal R.C.V. was 2564 ml. Eleven weeks after operation the R.C.V. was 2468 ml.

Plasma-iron Turnover (see table I)

In each case before operation the plasma-^{59}Fe half-clearance time was shortened (54 minutes and 28 minutes) while the turnover of iron through the plasma was increased (0·80 and 1·20 mg. per 100 ml. blood per day). Eleven weeks after nephrectomy the plasma-^{59}Fe half-clearance times had returned to normal (75 and 72 minutes) and so had the plasma-iron turnover (0·75 and 0·64 mg. per 100 ml. blood per day). The change in plasma-iron turnover was much greater in case 2 than in case 1.

Erythropoietin (see table II)

Before nephrectomy the plasma-erythropoietin activity was raised to 8 times normal in case 1 and 43 times normal in case 2. The erythropoietin levels eventually became normal after removal of the diseased kidney.

In case 1 blood samples were obtained at operation from the left renal vein (the side of the hydronephrosis), from a peripheral arm vein, and the aorta. The peripheral venous erythropoietin level was elevated to the same degree as in the preoperative specimens (8 times normal). The aortic and left renal venous samples, however, contained much less erythropoietin activity (twice normal).

Discussion

The essential feature of polycythæmia is an increased total red-cell volume, and Lawrence (1955) has stressed the danger of diagnosing polycythæmia on hæmoglobin concentration, hæmatocrit, or red-cell counts when these are not grossly abnormal. Even when the red-cell volume is known the significance of borderline values may be difficult to decide since the normal red-cell volume of a given subject cannot be predicted from his weight with any accuracy. Muldowney (1957) has shown that the

TABLE II—ERYTHROPOIETIN ASSAYS BEFORE AND AFTER OPERATION

Case no.	Time	Site of blood sample	Erythropoietin level (times normal)*
1	2 weeks preop.	Antecubital vein	8
	At op.	" "	8
		Lt renal vein	2
		Aorta	2
	4 weeks postop.	Antecubital vein	3
	16 weeks postop.	" "	1
2	2 weeks preop.	" "	43
	11 weeks postop.	" "	8
	19 weeks postop.	" "	1

* 95% confidence limits 60–160%; this implies that 95 times in 100 the true mean would lie within these limits.

fat-free body mass (lean body mass) is a much more accurate parameter for red-cell volume, and we have confirmed this relationship (Hyde and Jones 1960). The red-cell volumes in our 2 subjects were therefore related to lean body mass (see fig. 2). The results show that in each case there was initially a true increase in the circulating red-cell volume. Eleven weeks after nephrectomy case 2 had a normal red-cell volume. Four weeks after nephrectomy case 1 had a red-cell volume which was only 90 ml. above the upper limit of normal, compared with a preoperative value which exceeded this limit by 760 ml. At this time the plasma-erythropoietin level had not yet returned completely to normal. The operation was virtually bloodless in each case, and no other specific therapy was given.

In each case reported here the plasma-iron turnover was initially increased but became normal after nephrectomy. This change reflects the postoperative fall in red-cell production that may be inferred from the return to normal of the red-cell volume, hæmoglobin concentration, hæmatocrit, and plasma-erythropoietin level.

Gardner and Freymann (1958) concluded from a survey of published reports that the percentage of plasma-iron removed per hour (i.e., the ^{59}Fe-disappearance-rate constant $\times$ 100) was significantly greater in polycythæmia vera (209·7% $\pm$ 96·9%) than in secondary (anoxæmic) polycythæmia (79·5% $\pm$ 29·6%). In the case of polycythæmia with hydronephrosis reported by these workers the percentage of plasma-iron removed per hour was 210, thus resembling polycythæmia vera in this respect. In the 2 cases we report the corresponding figures were 77% and 149%, the first being within the range cited for secondary polycythæmia while the second resembles more closely that for polycythæmia vera. It does not seem likely that this parameter will prove a useful one with which to contrast primary and renal polycythæmia.

The existence of one or more humoral factors (erythropoietin) controlling erythropoiesis is now widely recognised, and it has been shown that plasma-erythropoietin levels are raised in polycythæmia vera (Contopoulos et al. 1957, Linman and Bethell 1957). An increasing body of experimental work suggests a close relationship between the kidney and plasma-erythropoietin (Jacobson et al. 1957, Goldwasser et al. 1958, Naets 1958, Osnes 1958, Lange et al. 1959). The plasma-erythropoietin level is not raised in the anæmia of chronic renal failure (Lange et al. 1959), whereas erythropoietin levels are elevated in most other anæmias (Piliero et al. 1956, Gordon 1959). This difference has been taken as evidence that the anæmia of chronic renal failure results from inadequate production of erythropoietin by the damaged kidneys.

Previous studies of renal polycythæmia have not included measurements of erythropoietin. In the present 2 cases the elevated erythropoietin levels and the subsequent fall to normal after nephrectomy further support the concept of an intimate relationship between plasma-erythropoietin and the kidney.

Much of the above work suggests that in certain pathological conditions the kidneys may produce increased amounts of erythropoietin. However, Hirsjärvi (1955, 1958) has reported experiments indicating a peripheral activation, or formation, of erythropoietin. The finding in case 1 that the venous blood draining from the hydronephrotic kidney had a lower erythropoietin level than blood from an arm vein is further evidence of such a peripheral mechanism. How some kidney lesions might affect this remains uncertain and further work is needed to clarify the relationship between the kidney and erythropoietin.

The association of polycythæmia with renal carcinoma has been reported in at least 34 cases (see Damon et al. 1958 and Forssell 1958). In a series of 205 patients with polycythæmia, Damon et al. (1958) found 9 cases of renal carcinoma (an incidence of 4·4%). Lawrence and Donald (1959) found that renal carcinoma occurred in 0·93% of a series of 325 polycythæmic patients, whereas the expected incidence of renal carcinoma in America is 0·003%. These figures suggest that this association is not fortuitous. The long remissons of the polycythæmia that have followed successful nephrectomy is further evidence for this conclusion.

Coexistent polycythæmia and non-neoplastic renal disease have been reported to date in 10 cases (see table III). The numbers of any one type of renal lesion are as yet too small to exclude a chance association, and the true prevalence of kidney disease associated with polycythæmia remains unknown. Increasing awareness of this syndrome may well lead to more frequent recognition. It is interesting that in 3 of the 6 cases with polycystic kidneys this condition was unilateral.

In addition to the 2 cases reported here the results of nephrectomy in polycythæmia associated with non-neoplastic renal lesions are available in 4 other patients, and in each case remission of the polycythæmia has occurred. In 3 of these cases (including both our patients) no other specific therapy was given. These facts are further evidence of a causal relationship between certain renal lesions and polycythæmia.

TABLE III—DETAILS OF REPORTED CASES WITH POLYCYTHÆMIA AND NON-NEOPLASTIC RENAL DISEASE

Source	Renal disease	Age (yr.)	Sex	Hb (g. per 100 ml.)	P.C.V. (%)	Red cells ($\times 10^6$)	Red cell volume (ml. per kg.)	Blood-volume	White cells (per c.mm.)	Platelets (per c.mm.)	Palpable spleen	Blood-pressure (mm. Hg)	Nephrectomy	Remission after nephrectomy‡	Other therapy
Cooper and Tuttle (1957)	Hydronephrosis	55	M	19·0	68	..	..	7750 ml.	11,300	360,000	No	150/100	Yes	6 yr.	V*
Gardner and Freymann (1958)	„	65	M	21·4	68	6·88	40·9	70·2 ml. per kg.	11,050	Normal	No	190/120	Yes	2 yr.	V*
Lawrence and Donald (1959)	„	37	M	23·0	..	9·60	..	..	10,700	750,000	No	140/95	Yes	18 mos.	V*, ^{32}P
Present case 1	„	57	M	21·8	62	6·80	39·0	84·5 ml. per kg.	9,900	171,000	No	210/120	Yes	6 mos.	..
Present case 2	Polycystic rt kidney	55	M	18·8	57	6·60	33·2	66·0 ml. per kg.	13,100	185,000	No	160/90	Yes	7 mos.	..
Kurrle (1954)	Polycystic kidneys	42	M	144%	..	9·0	..	..	10,400	452,000	No	200/130	No	..	V*, ^{32}P
Forssell (1958)	Polycystic rt kidney	61	M	126%†	..	6·28	..	..	7,200	136,000	No	Elevated	Yes	2½ mos.	..
„ „	Polycystic kidneys	32	M	141%†	74	8·10	..	9329 ml.	Normal	Normal	Yes	Elevated	No	..	..
„ „	Polycystic rt kidney	61	F	139%†	70	7·24	..	7480 ml.	12,000	400,000	No	Elevated	No	..	..
„ „	Polycystic kidneys	57	M	141%†	71	7·42	..	8267 ml.	Normal	Normal	No	Elevated	No	..	..

* Venesection. † Sahli. ‡ To date of publication.

In polycythæmia vera increased white-cell and platelet counts are common, while the spleen is usually palpable at some stage of the disease. Damon et al. (1958) concluded that most patients with polycythæmia and renal carcinoma lack splenomegaly, leucocytosis, and thrombocytosis, so that the "polycythæmia" is more properly termed "erythrocytosis". The data in table III suggest that in polycythæmia associated with non-neoplastic renal lesions the spleen is usually impalpable and the platelet count usually normal. White-cell counts greater than 10,000 per c.mm. were obtained in 6 of the 10 cases, but the figures cited are the highest obtained in each case and all may be within normal limits. The results of bone-marrow examination are available in 7 of the 10 cases, and, whereas increased erythropoiesis was noted in 5 cases, no mention is made of excessive myeloid activity. The available data are insufficient to decide whether hypertension is more common in renal polycythæmia than in polycythæmia vera. In summary, renal polycythæmia is usually characterised by an erythrocytosis with normal platelet and white-cell counts while the spleen is impalpable.

Certain practical implications follow from the recognition of this syndrome of renal polycythæmia. The possibility of an underlying renal lesion should be considered in any polycythæmic patient, especially when white-cell and platelet counts are normal, and the spleen cannot be felt. Examination of the urine, palpation of the loins, and intravenous pyelography should be undertaken in such a case. Hæmaturia has sometimes been attributed to an abnormal bleeding tendency in polycythæmia. Hæmaturia occurred, however, in most of the reported cases of polycythæmia with renal disease, and its occurrence should intensify the search for a renal lesion. Because the polycythæmia may remit after nephrectomy, diagnosis of the kidney disease in renal polycythæmia is especially important.

Summary

In 2 cases of polycythæmia—1 associated with hydronephrosis and the other with a unilateral polycystic kidney—the polycythæmia disappeared after removal of the renal lesions.

Plasma-erythropoietin levels were raised before operation but fell to normal after nephrectomy.

Plasma-iron turnover was initially increased but returned to normal after nephrectomy.

The features of this type of polycythæmia and the part played by the kidney in the control of erythropoiesis are discussed.

The syndrome of renal polycythæmia is probably commoner than is realised. Diagnosis of the renal lesion is important because its removal may lead to remission of the polycythæmia.

We wish to thank Dr. G. Wetherley-Mein and Dr. Brian Creamer for much useful advice; Prof. F. T. G. Prunty and Dr. J. L. Pinniger, for encouragement and permission to investigate these patients in the William Dunn and Louis Jenner Laboratories; and Dr. R. Daley and Dr. Evan Jones, who allowed us to study and to report their patients.

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EFFECT ON THE KIDNEY OF DRUGS CONTAINING PHENACETIN

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As early as 1950, Spüler and Zollinger in Switzerland drew attention to a chronic interstitial nephritis which they suggested was due to prolonged abuse of phenacetin-containing analgesics, since a very great proportion of their patients had been addicted to these preparations (Spüler and Zollinger 1953).

In attempts to reproduce the syndrome by animal experiments and to determine the significance of phenacetin, Studer and Zbinden (1955) demonstrated slight degeneration of the tubules but no genuine interstitial nephritis in rats given large doses of 'Saridone' for long periods. On the other hand, Thölen et al. (1956) were able to produce interstitial nephritis in corresponding experiments in mice, possibly because in these animals spontaneous urinary infection with *Clossiela muris* is common. Moreover, Miescher et al. (1958) produced interstitial nephritis in rabbits by feeding them with phenacetin and simultaneously giving *Escherichia coli* intravenously (injection of *Esch. coli* in a control group did not produce renal injury).

Direct provocation experiments are probably necessary to demonstrate the relation of phenacetin to chronic interstitial nephritis in man. In a series of patients who had abused phenacetin and whose renal function was reduced, we therefore undertook direct provocation experiments with pure phenacetin and with phenacetin contaminated with acetic-4-chloranilide (preparations of phenacetin usually contain this contaminant). Quantitative changes in the urinary sediment were used as a measure of renal irritation.

Effects of Provocation

11 patients were given phenacetin entirely free from acetic-4-chloranilide, 8 patients had phenacetin containing 0·13% acetic-4-chloranilide, and 8 phenacetin containing 0·30% acetic-4-chloranilide. For three days, all drugs were withdrawn and then the patients received 3 g. daily of the phenacetin preparation for five days. Both in the preliminary period and the five days of the experiment, sediment counting by

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TABLE I—ERYTHROCYTE-COUNT IN TWELVE-HOUR URINE

Patient	Red cells (millions)							
	Control period			During treatment with 3 g. pure phenacetin per day				
	1st day	2nd day	3rd day	1st day	2nd day	3rd day	4th day	5th day
1	..	3·7	7·3	9·1	2·3	7·7	1·0	..
2	7·4	3·9	1·2	2·6	3·7	2·9	1·2	1·0
3	9·2	0·5	1·1	4·5	3·0	2·4	0·6	0·4
4	1·7	0·9	0·9	0·9	1·3	2·4	3·0	4·2
5	5·6	7·0	5·4	4·5	20·1	6·0	2·6	3·2
6	1·0	0·2	0·4	0·3	0·3	0·4	0·1	0·3
7	3·4	2·3	13·9	11·6	3·1	5·9	3·1	..
8	0·8	0·6	0·6	1·0	1·8	1·7	1·5	..
9	0·7	1·2	3·7	2·6	1·8	2·4	0·7	..
10	0·5	0·8	0·9	0·5	0·9	0·8	0·4	0·6
11	0·1	0·0	0·4	0·5	0·6	0·3	0·5	1·1
				During treatment with 3 g. phenacetin per day containing 0·13% acetic-4-chloranilide				
12	1·5	2·5	1·7	0·7	2·3	1·8	1·1	2·1
13	0·9	0·6	1·2	14·5	1·9	1·6	2·2	1·1
14	0·2	1·2	0·3	1·2	1·3	1·4	1·7	1·0
15	0·6	0·5	0·5	1·2	0·5	1·2	0·8	..
16	0·1	0·0	0·2	0·4	0·2	0·7	0·4	0·3
17	9·4	3·7	4·2	5·7	3·5	4·6	2·0	3·0
18	0·4	0·4	0·5	0·1	0·4	0·2	0·6	0·5
19	0·2	0·1	0·3	0·4	0·6	0·8	0·8	0·6
				During treatment with 3 g. phenacetin per day containing 0·30% acetic-4-chloranilide				
20	0·0	0·1	0·1	0·0	0·0	0·3	0·2	..
21	0·2	0·1	0·2	0·2	0·3	0·8	0·4	1·0
22	1·0	0·8	1·2	1·8	1·1	2·2	1·1	1·5
23	0·3	0·1	0·2	0·4	0·1	0·2	0·2	0·2
24	0·1	0·1	0·2	0·2	0·2	0·2	0·2	0·2
25	0·1	0·1	0·0	0·3	0·1	0·2	0·1	0·1
26	0·5	0·1	0·3	1·0	0·2	0·6	0·3	0·3
27	1·8	1·3	5·3	2·6	5·3	6·2	1·1	7·1

TABLE II—LEUCOCYTE-COUNT IN TWELVE-HOUR URINE

Patient	White cells (millions)							
	Control period			During treatment with 3 g. pure phenacetin per day				
	1st day	2nd day	3rd day	1st day	2nd day	3rd day	4th day	5th day
1	..	203·9	325·6	1054·8	383·6	354·2	246·7	..
2	7·7	7·0	9·7	11·6	23·3	15·3	12·7	15·4
3	352·1	493·9	456·1	567·4	899·6	288·4	422·3	501·6
4	30·2	26·8	39·9	34·2	37·6	45·2	34·9	43·3
5	259·2	281·4	212·2	291·7	321·0	291·0	344·1	330·9
6	8·9	3·0	6·9	2·0	5·4	5·0	2·1	3·9
7	766·7	846·3	1179·7	900·9	693·5	660·1	241·0	..
8	22·3	17·6	22·5	23·9	32·2	18·9	52·6	..
9	69·2	61·9	170·6	103·4	50·9	82·2	45·5	..
10	6·5	9·8	13·0	6·4	17·0	9·3	6·0	..
11	0·6	0·3	0·4	0·4	1·6	0·4	1·1	2·2
				During treatment with 3 g. phenacetin per day containing 0·13% acetic-4-chloranilide				
12	1383·5	1423·9	814·1	538·0	455·2	752·3	426·1	525·7
13	24·2	16·4	7·4	42·6	11·1	15·7	24·8	12·6
14	0·4	0·5	0·6	0·6	1·3	0·1	0·9	0·5
15	3·4	4·4	4·6	12·0	12·4	17·3	8·8	..
16	1·7	4·2	5·6	6·5	4·0	7·6	12·3	19·9
17	31·3	40·6	43·0	108·9	48·8	86·2	27·2	70·9
18	26·5	41·1	26·4	16·8	13·6	18·7	41·4	20·6
19	1·3	1·1	5·3	5·4	7·5	14·1	4·0	5·3
				During treatment with 3 g. phenacetin per day containing 0·30% acetic-4-chloranilide				
20	1·0	11·0	6·2	2·9	1·8	0·4	4·2	..
21	55·3	76·3	75·7	84·3	73·3	54·7	299·8	286·7
22	209·9	169·1	154·0	154·7	161·3	174·2	217·4	163·8
23	18·0	5·4	5·6	4·7	4·2	3·7	1·5	3·6
24	1·5	3·7	4·0	1·6	4·8	7·4	5·0	10·2
25	0·7	0·6	0·4	0·5	1·0	1·1	1·4	0·5
26	72·6	104·9	122·2	76·4	111·3	95·5	443·5	68·9
27	171·7	194·6	123·6	103·4	315·8	244·5	149·5	320·8

the Addis method was undertaken daily on a twelve-hour sample of night urine to which toluol was added as preservative. The urinary sediments were counted immediately after collection of urine, and all counts were undertaken by one laboratory worker, experienced in the technique. In the analysis, only the erythrocyte and leucocyte values were considered.

The erythrocyte and leucocyte counts recorded are shown in tables I and II.

Probably because of the inexactitude of the counting method, the scatter of the twenty-four-hour values is great, so that the considerable variations from day to day make it hard to see directly whether the sediment values are higher than usual during provocation with phenacetin in individual patients. It proved suitable in the statistical analysis to use logarithmic values for the urinary sediments since the standard deviation of the logarithms, by and large, seemed to be independent of the absolute quantity of the urinary sediment in the individual patients. For each of the preparations of phenacetin the average logarithm of the sediment values in the preliminary period was compared with the corresponding value in the treatment period. The results of the statistical analysis were shown in table III.

A significant increase in the erythrocyte-count in the urinary sediment was found during treatment with both of the preparations containing acetic-4-chloranilide; on the other hand, a significant increase in the leucocyte-count was recorded only in the experiment in which phenacetin with 0·13% acetic-4-chloranilide was used. With pure phenacetin the increase in the erythrocyte-count was approximately 15% and in the leucocyte-count approximately 11%, but these differences were not significant.

Discussion

The results support the view that phenacetin-containing preparations may damage the kidney. Preparations containing acetic-4-chloranilide may be chiefly responsible, since the quantitative change in the urinary sediment is much more pronounced with them than with purified phenacetin. The observation that the effect of the most markedly contaminated preparation was less than that of a purer preparation may be explained by the fact that the patients in the last series had better renal function than those in the first two series. The degree of renal irritation may partly depend on the patients' renal function, being greatest when function is poor.

As Hald (1950) showed, the preparations of phenacetin at present available contain varying quantities of acetic-4-chloranilide as a contaminant. Analysis of 22 preparations of phenacetin revealed contamination varying from 0·02 to 0·64%. The *Danish Pharmacopœia*, which, with the exception of the *British Pharmacopœia*, is the only one to give directions on this subject, permits a maximum of 0·35% acetic-4-chloranilide. Acetic-4-chloranilide is a much more potent former of methæmoglobin than phenacetin (Gad et al. 1950), and the question arises whether abnormal hæmoglobin products may be responsible for the renal damage.

Phenacetin was originally manufactured by synthesis from 4-nitrophenol, and contamination with acetic-4-chloranilide did not occur. For twenty or twenty-four

TABLE III—COMPARISON BETWEEN URINE COUNTS BEFORE AND DURING TREATMENT WITH PHENACETIN

—	Mean of logarithms of absolute urine counts		Difference	t-value
	Control period	During treatment		
Erythrocytes:				
Pure phenacetin ..	0·139	0·201	0·062	0·97
Phenacetin with 0·13% acetic-4-chloranilide	−0·204	0·009	0·213	2·84*
Phenacetin with 0·30% acetic-4-chloranilide	−0·611	−0·411	0·200	2·67*
Leucocytes:				
Pure phenacetin ..	1·585	1·631	0·046	1·02
Phenacetin with 0·13% acetic-4-chloranilide	1·051	1·202	0·151	2·85*
Phenacetin with 0·30% acetic-4-chloranilide	1·249	1·248	−0·001	−0·02

* $0{\cdot}01 > P > 0{\cdot}001$.

years, however, phenacetin has been prepared from 4-nitrochlorbenzol, with acetic-4-chloranilide as a by-product. This change may explain why the toxic action of phenacetin-containing preparations was detected only in recent years.

Summary

In recent years suspicion has arisen that chronic abuse of phenacetin and phenacetin-containing analgesics may cause severe renal damage. The nephrotoxic effect of phenacetin was estimated in 27 addicts by quantitative determination of the urinary sediment by the Addis method.

In 11 patients given purified phenacetin, a slight but not significant rise was registered; in 16 patients given phenacetin contaminated with acetic-4-chloranilide (a contaminant found in varying amounts in practically all preparations of phenacetin) the effect was much more pronounced, with significant rise in both erythrocyte and leucocyte counts. As acetic-4-chloranilide is a much stronger former of methæmoglobin than phenacetin, renal damage may be caused by the abnormal hæmoglobins, and not by a direct toxic effect of phenacetin or related drugs.

We wish to express our gratitude to Dr. Jens Hald, of Meco-Dumex Ltd. (former Medicinalco Ltd.), for the interest taken in our work and for the suggestion that we examine the effect of acetic-4-chloranilide-containing drugs. We also wish to thank Miss Inger Ladegård for technical assistance. The work was supported by a grant from King Christian X's Fund.

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SPEED OF ACTION OF ASPIRIN, SOLUBLE ASPIRIN, AND BUFFERED ASPIRIN

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ASPIRIN (acetylsalicylic acid) is probably the most widely prescribed drug in this country. In 1954 3000 million tablets of aspirin were produced in the United Kingdom. Recently various proprietary brands of acetylsalicylic acid have been recommended as having a faster action or fewer side-effects; but there seems to be no conclusive evidence in favour of these claims.

Aspirin is absorbed from the stomach of dogs with the pylorus ligated, but it is absorbed most quickly from the intestine (P. K. Smith 1949). Any factor which influences gastric emptying may therefore be expected to influence aspirin absorption correspondingly. Bradley et al. (1936) showed that aspirin itself caused an increase in gastric secretion and delay in gastric emptying, but whether it acts locally or by way of a central stimulus of gastric secretion is unknown (*British Medical Journal* 1952).

M. J. H. Smith (1951) gave 6 subjects aspirin *B.P.* and a proprietary aspirin, and found higher serum levels with the proprietary preparation. Paul et al. (1950) similarly compared a buffered aspirin with aspirin *U.S.P.* and concluded that the buffered aspirin gave serum levels twice as high at 10 and 20 minutes after administration, but in their trial the two drugs were not compared in the same subjects. More recently Cronk (1958) and Batterman (1958) compared buffered aspirin with a rapidly disintegrating non-buffered aspirin and found no significant differences after gr. 10 doses in cross-over trials involving 9 and 20 subjects. No mention is made of the method of administration of the tablets except that they were given by mouth.

The present study concerns the speed of absorption of aspirin in normal subjects free from gastrointestinal disease, under strictly controlled conditions. Each subject was given aspirin *B.P.*, soluble aspirin *B.P.* (calcium aspirin), and two proprietary preparations—namely, acetylsalicylic acid plus aluminium carbonate and magnesium carbonate in small amounts ('Bufferin'), and acetylsalicylic acid plus glycine ('Paynocil').

Methods and Materials

There are several established methods for the estimation of plasma salicylate, the best-known being that of Brodie et al. (1944). These, however, were developed mainly for measuring the high values occurring during the treatment of acute rheumatism, and were not easily applicable to the low serum levels of this trial. Also, they involved the use of the toxic substance ethylene dichloride. M. J. H. Smith (1951) described a method for this type of study and this has proved satisfactory in my hands. It was used unmodified except that the instrument used was a Cambridge 'Unicam' S.P. 600 with the red cell transmitting at 750 μ. For serum levels below 10 mg. per 100 ml. the variation due to the method was less than 0·5 mg. per 100 ml.

Six healthy volunteers (aged 20–33) who had not taken any salicylate in the previous 72 hours were given gr. 10 doses of aspirin in the four forms, using a double-blind technique. The tablets, aspirin *B.P.*, calcium aspirin *B.P.*, paynocil, and bufferin were obtained and prepared by the hospital pharmacist and labelled A, B, C, and D; their identity was not revealed to the investigator until the statistical analysis had been made. The tablets were given in predetermined random order using the method of roman squares—i.e., the six subjects received the tablets A, B, C, and D in a different order. This ensured that a given tablet was not always administered first or last and that on any particular day the tablets were being estimated side by side, eliminating as far as possible any bias due to variation in experimental conditions.

The tablets were given under standard conditions 2 hours after the subject's normal breakfast. As stated previously, earlier trials have given little information on the method of administering tablets. If swallowed whole, a tablet which is slow to disintegrate is likely to be at a disadvantage compared with one which disintegrates rapidly. To avoid this discrepancy the tablets were crushed in 2 oz. of water and the glass was then rinsed twice in 2 oz. of water so that the dose was taken in a total of 6 oz. of water. The tablets differed considerably in the ease with which they were dispersed.

Blood was drawn by repeated venepuncture at 0, 10, 20, and 30 minutes, the time recorded being the moment of venous occlusion. Each time 15 ml. of blood was withdrawn smoothly by dry syringe into a heparinised bottle containing added fluoride. A pilot survey had shown that heparin caused no hæmolysis. When oxalate or citrate was used hæmolysis was only slight; but it proved troublesome because it led to high "blank" values in the zero-time specimens.

The collected specimens were then centrifuged and the serum-salicylate values estimated as mg. sodium salicylate per 100 ml., almost exactly convertible into mg. acetylsalycilic acid (molecular weight sodium salicylate=173, acetylsalicylic acid=180).

TABLE I—MEAN TOTAL SALICYLATE LEVELS (EXPRESSED AS MG. SODIUM SALICYLATE PER 100 ML.)

—	A Bufferin	B Soluble aspirin *B.P.*	C Paynocil	D Aspirin *B.P.*
10 minutes	2·3±1·02 (0·9–3·8) 6	3·2±1·9 (0·4–4·9) 6	2·4±1·12 (0·7–3 6) 6	1·3±0·57 (0·2–1·8) 6
20 minutes	4·8±1·01 (2·3–6·2) 6	5·4±2·01 (1·9–6·9) 6	4·0±1·57 (2·2–5·9) 6	2·7±1·08 (0·7–3·9) 6
30 minutes	5·4±1·03 (4·5–6·8) 4	5·3±1·35 (2·8–6 6) 6	4·6±1·57 (2·8–6·8) 6	3·3±1·09 (1·5–4·5) 6

Range in parentheses. Number of observations below.

Normal serum containing no salicylate gives a faint blue colour as compared with the reagent blank and this reading at zero time (varying with each patient but usually equivalent to about 0·5 mg. acetylsalicylic acid, or less, per ml.) was deducted from the readings obtained at the specified times to obtain the true salicylate levels at those times.

Calibration curves were done repeatedly during the period of the trial and did not appear to differ significantly. However, with each test a freshly prepared standard solution of 5 mg. aspirin per 100 ml. was run through in addition to the plasma and reagent blanks. Occasional values are missing—e.g., because of failed venepuncture, insufficient plasma, or obvious hæmolysis in one specimen of a batch; but in the statistical analysis these values have been taken into consideration.

The levels of serum acetylsalicylic acid are obtained from the differences between aliquots of serum at each time; one aliquot is estimated for free salicylate, the other for total salicylate after hydrolysis by caustic soda.

At the conclusion of the experiment random samples were taken from each of the original batches or tablets and analysed for total salicylate content. The variation in content between tablets in the same batch was of the order of five per cent and there was no consistent difference between the aspirin content of the different groups.

All venepunctures and all salicylate determinations were done by myself, thereby ensuring standard technique at all stages.

Results

Results are shown in tables I and II. The scatter between the values for each subject (figures in parentheses) mainly represents individual variation in the subjects themselves, since the variation due to the method was found to be usually less than 0·5 mg. per 100 ml.

Serum salicylate levels were much the same (table I) after taking bufferin, soluble aspirin *B.P.*, and paynocil, but considerably lower after taking aspirin *B.P.* The difference was significant at the 1% level at all times if aspirin is compared with the other three groups combined (see figure).

Plasma levels for acetylsalicylic acid differ little for the four aspirin preparations given (table II). The fact that they are all relatively low might be explained by partial failure of the fluoride present in the anticoagulant to inhibit the serum esterase concerned. Lester et al. (1946) found that an average of 25% of the total salicylate was present as acetylsalicylic acid. The proportion found here varied from 10–25% approximately.

TABLE II—MEAN PLASMA-ACETYLSALICYLIC-ACID VALUES (MG. %)

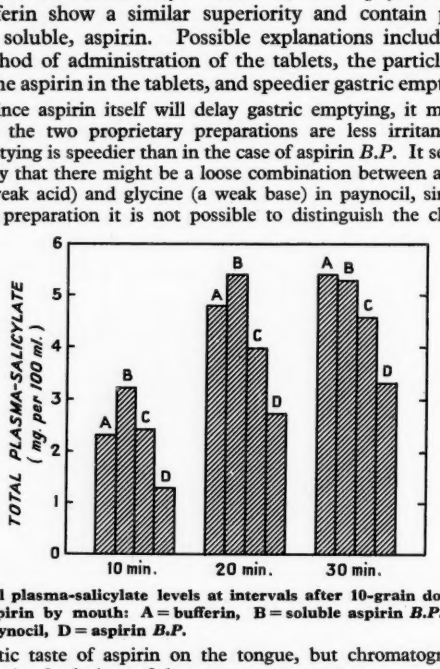
—	A Bufferin	B Soluble aspirin *B.P.*	C Paynocil	D Aspirin *B.P.*
10 minutes	0·5 (0–1·1) 6	0·3 (0–0·8) 6	0·5 (0–1·7) 4	0·2 (0–0·9) 5
20 minutes	0·9 (0–1·6) 6	0·6 (0–1·4) 5	1·0 (0·2–2·1) 5	0·5 (0–1·1) 6
30 minutes	0·5 (0–1·2) 4	0·3 (0–1·0) 6	0·9 (0·1–2·1) 5	0·8 (0–1·3) 6

Range in parentheses. Number of observations below.

Discussion

Judging by evidence from blood-levels, plain aspirin has been shown to be roughly half as rapidly effective as soluble aspirin. This difference might be expected from its known insolubility. However, both paynocil and bufferin show a similar superiority and contain plain, not soluble, aspirin. Possible explanations include the method of administration of the tablets, the particle size of the aspirin in the tablets, and speedier gastric emptying.

Since aspirin itself will delay gastric emptying, it may be that the two proprietary preparations are less irritant and emptying is speedier than in the case of aspirin *B.P.* It seemed likely that there might be a loose combination between aspirin (a weak acid) and glycine (a weak base) in paynocil, since in this preparation it is not possible to distinguish the characteristic taste of aspirin on the tongue, but chromatographic analysis of solutions of these two components gave no support for this theory. In the case of bufferin the present results confirm those of Paul et al. (1950) and are at variance with those of Cronk (1958) and Batterman (1958) who found no difference between bufferin and a rapidly disintegrating proprietary aspirin.



Total plasma-salicylate levels at intervals after 10-grain doses of aspirin by mouth: A = bufferin, B = soluble aspirin *B.P.*, C = paynocil, D = aspirin *B.P.*

The presence of acetylsalicylic acid in the serum has been demonstrated again (Lester et al. 1946, Smith 1951, Mandel et al. 1954). Normally, significant quantities of the drug remain only for two to three hours (Gross and Greenberg 1948), because of its rapid hydrolysis to sodium salicylate by serum esterase. The fact that aspirin is more diffusible than plain salicylate, because less of the former is protein-bound in the serum, probably explains the therapeutic superiority of aspirin over plain salicylate. The clinical corollary of this is that, if aspirin is to be used logically it should not be said to be ineffective unless it has been taken at short intervals (i.e., two- or three-hourly). This is particularly important in the relief of long-continued pain as in rheumatoid arthritis.

The present trial demonstrates that under standard conditions calcium aspirin *B.P.* was as effective in giving rapid blood-levels as two proprietary buffered aspirins (paynocil and bufferin) but that all three were superior to plain aspirin *B.P.* The relative costs to the hospital service of these three drugs are:

Aspirin *B.P.* = 0·12*d.* for 10 grains aspirin
Soluble aspirin *B.P.* = 0·22*d.* „ „ „ „
Buffered aspirin (paynocil) = 0·54*d.* „ „ „ „
„ „ (bufferin) = 1·1*d.* „ „ „ „

The superiority of calcium aspirin over plain aspirin in the rapid achievement of demonstrable blood-levels is stressed. If in addition account is taken of the evidence incriminating plain aspirin as a cause of serious side-effects such as gastrointestinal hæmorrhage (Muir and Cossar 1955), its continued use appears questionable.

Summary

Blood-levels of acetylsalicylic acid and salicylate obtained at 10, 20, and 30 minutes after gr. 10 doses of aspirin *B.P.*, soluble aspirin *B.P.*, and two buffered preparations paynocil and bufferin were compared.

Soluble aspirin *B.P.* gave approximately twice the blood-levels of aspirin *B.P.* at these times and equal levels were obtained with paynocil and bufferin, both of which were similarly superior to plain aspirin *B.P.* Suggested explanations are diminished local irritation and consequent speedier gastric emptying when soluble or buffered aspirins are used.

The presence of unchanged acetylsalicylic acid is again demonstrated in serum and the significance of this discussed, with particular reference to the point that aspirin therapy cannot be said to have failed unless the drug has been taken at two- or three-hourly intervals.

I am grateful to Dr. Kenneth Robson, who originally suggested the study, and to Dr. J. C. Batten, for advice and encouragement; to Prof. J. Knowelden for help with the statistical planning of the trial; and to Mr. G. Franglen for carrying out the chromatography and assisting with the statistical calculation.

I wish to acknowledge a grant from the research committee of St. George's Hospital towards expenses.

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BISALBUMINÆMIA

A HEREDITARY ALBUMIN ABNORMALITY

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Knedel (1957, 1958) reported an abnormal protein in the serum of a 15-year-old girl with hepatitis. Her sister, her mother, her maternal grandmother, and a maternal uncle all had a similar anomaly. The sera from two cousins (a daughter and son of the uncle) did not contain demonstrable amounts of the anomalous protein. From its electrophoretic and immunological behaviour, Knedel thought the protein was an albumin. Other families with a similar anomaly have been reported by Nennsteil and Becht (1957), Wuhrmann (1958), Bennhold, Ott, and Scheurlen (1958) and Earle, Hutt, Schmid, and Gitlin (1958, 1959).

Case-report

A boy of 16 was seen in the skin department of King's College Hospital last August, with a curious condition of the hands. These had always been cold and blue even in summer. In the previous three years there had been an increasing flexural deformity of the fingers—first of the little fingers, and later, to a lesser degree, the ring, middle, and index fingers of one hand. It was difficult to account for his inability to straighten these fingers: there was no sclerosis of the skin, nor, apparently, any involvement of fascia or tendons. The horny layer over the knuckles was slightly thickened and a slight mosaic of hyperkeratosis could be seen in the nailfolds. The condition was clearly not acrosclerosis nor any form of Raynaud's phenomenon. The boy's father had similar hands but could straighten his fingers normally. The paternal grandfather (deceased) was said to have had cold blue hands.

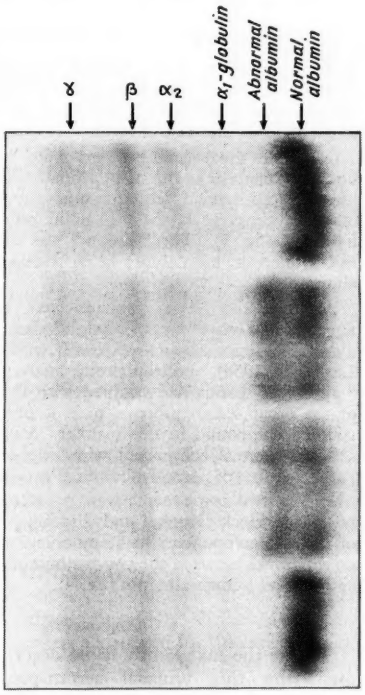


Fig. 1—Electrophoretic demonstration of second component in region of albumin.

Investigations

In the course of various laboratory investigations paper-electrophoretic analysis of the serum proteins revealed, in both father and son, a distinct double band in the region of the albumin. The sera were submitted to an independent laboratory for confirmation and further study. There, among other investigations, electrophoresis was carried out on filterpaper and in agar against known albumin controls and by the classical moving boundary method of electrophoresis. The presence of a second component in the region of the albumin was confirmed (fig. 1). Sera from the other members of the family were collected and examined. As in the family reported from America, the genetic pattern (fig. 2) seems to be that of a dominant heterozygote.

We have assumed that the faster of the two " albumin " components is that normally seen in electrophoretic analysis. We believe that the second peak represents an albumin, for the following reasons:

1. (*a*) Zone electrophoresis on paper, cellulose acetate, and agar all displayed a well-defined double band having a mobility similar to that of albumin and faster than that

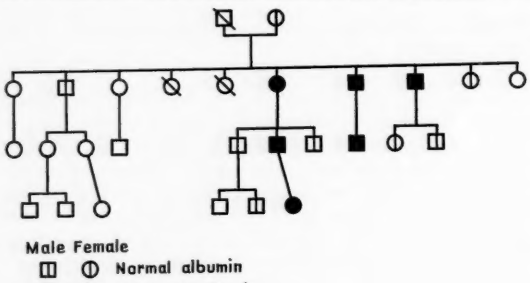


Fig. 2—Pattern of inheritance.

of the α_1-globulin in the control normal serum. Moreover α_1-globulin could be identified, clearly separated from the abnormal "albumin", having a mobility similar to the α_1-globulin in the control serum.

(*b*) When the serum proteins were subjected to moving-boundary analysis in 0·2 *M* phosphate buffer at pH 8·0 for six hours, a well-defined "hump" was seen on the posterior slope of the albumin peak, the α-globulin being clearly discernible behind it (fig. 3). The "hump" was constant on prolonged electrophoresis, its mobility being within the range of normal albumin.

2. When the serum proteins were exposed in buffered aqueous solution to *n*-tolyl-α-naphthylamine-8-sulphonic acid, a dye believed to couple specifically with albumin (Weber and Lawrence 1954), electrophoretic analysis showed that both "albumin" bands had coupled with the dye and that none of the other serum proteins present produced a fluorescent-coupled compound in this manner. Moreover the behaviour of the abnormal component with sulphonphthalein dyes also paralleled that of normal albumin (Franglen 1958).

3. The two components were separated by electrophoresis on starch block (Kunkel and Trautman 1959). Comparison of the two components by immunological techniques showed no difference between the two "albumins" nor between them and normal human albumin (fig. 4).

Discussion

This is the first family to be described in this country displaying this unusual serum-protein anomaly—the eighth, so far as we can ascertain, in the world literature. In none of the other families has the anomaly been shown to be associated regularly with any other demonstrable defect, most of the members being in perfectly good health.

In the present family the peculiar dermatological condition was noted in father and son. There is evidence that the grandfather also suffered from "cold blue hands". As we could not demonstrate the split albumin in the grandmother, it is reasonable to suppose that this defect was transmitted through the grandfather. While it is tempting to link the unusual skin condition with the protein abnormality, we must admit that four other members (two female and two male) showing the split albumin had no dermatological defect.

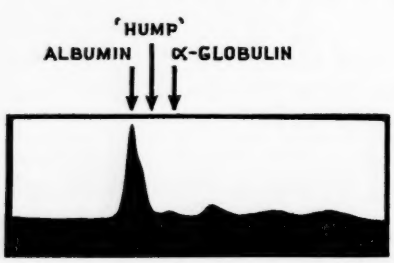
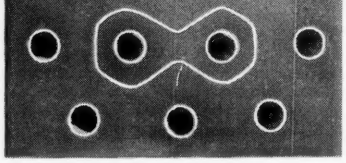


Fig. 3—Hump on posterior slope of albumin peak.

Preliminary studies have shown no striking deviations in the aminoacid analysis of the abnormal albumin. If we assume that the shape and size of this component does not differ markedly from normal albumin, the electrophoretic analyses suggest that the net surface charge of the molecule is very near to that of normal albumin.

Bergstrand and Czar (1956, 1957) described a protein migrating between albumin and α_1-globulin in the serum from fœtuses up to the 19th week, obtained from legal abortions. They reported this component to be about 10% of the normal albumin present. Such quantitative studies as we have made suggest that the abnormal albumin which we are now describing represents about 50% of the total albumin and that this proportion is remarkably constant—a finding similar to that of Earle et al. (1959). In thalassæmia (another hereditary protein dyscrasia) the fœtal type of hæmoglobin persists in varying amounts in different members of the family. Though it is tempting to propose that our abnormal albumin represents a persistence of the fœtal component described by Bergstrand and Czar, the condition differs from thalassæmia in one striking respect — namely, that all the members of the family we have examined, extending through four generations, have shown the component at a level of 50% of the total serum-albumin or else none at all.



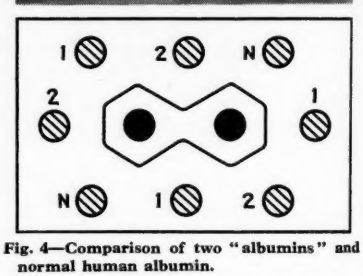


Fig. 4—Comparison of two "albumins" and normal human albumin.

Summary

In a family followed through four generations a bifid albumin occurs as a dominant heterozygous character. Reasons are given for regarding the abnormal component as albumin, and a comparison is drawn with thalassæmia.

In three successive generations an unusual skin condition was observed in three of the seven members of a family believed to be suffering from the protein dyscrasia.

G. Franglen and N. H. Martin acknowledge with gratitude financial support from the free funds of St. George's Hospital.

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THE THORN IN THE FLESH

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IN 1787, two years after publishing An Account of the Fox-Glove and Some of its Medical Uses, William Withering, writing about *Prunus spinosa* (blackthorn or sloe-tree) noted that "the thorns have something of a poisonous nature in the autumn". In 1801 he confirmed this observation: "From some effects which I have repeatedly observed to follow the prick of the thorns, I have reason to believe there is something poisonous in them . . ."

I have recently observed and treated ten patients with this injury. No other similar series has been reported in English.

Most of the patients were agricultural workers, and, as might be expected, all the injuries were in the hand. There was no particular seasonal incidence.

The average interval between time of injury and first visit to the accident service was 8·7 days; and the average duration of outpatient treatment was 45 days. By comparison, 60 patients with other thorn injuries—e.g., rose, hawthorn, gooseberry, &c., or unspecified—were treated as out-patients for an average of 11·9 days.

Illustrative Case

A 67-year-old thatcher injured his left index finger with a blackthorn at the end of January, 1958. Next day "the finger started swelling and throbbing," and on the day after that his doctor started him on a week's course of tetracycline. At the end of the week he was able to resume work, but 2 days later his symptoms recurred and he was given intramuscular penicillin one mega-unit daily for 7 days. "The finger settled and the swelling went down", but symptoms returned when he had been back at work for 2 days.

After a sleepless night he was first seen by us on Feb. 13. He did not look ill and was apyrexial. His left index finger showed minor occupational scarifications in addition to the blackthorn puncture wound on the flexor aspect of the proximal interphalageal joint. Swelling and tenderness were greatest over the proximal flexor pulp; there was no lymphangitis or lymphadenitis.

Under general anæsthesia the proximal pulp space was explored. The flexor tendon sheath proved to be thickened and tense. The sheath was opened; its thin yellow contents were evacuated, together with some "melon-seed bodies"; and the granulomatous material associated with the thickened tendon sheath was excised. Skin sutures were inserted and the finger splinted with a plaster slab.

The contents of the tendon sheath showed many pus cells and occasional gram-positive cocci. No acid-fast bacilli were seen (Ziehl-Nielsen). Culture gave a light growth of micrococci and diphtheroids but no tubercle bacilli. The granulomatous material was described as "vascular granulation tissue with a dense polymorphonuclear exudate".

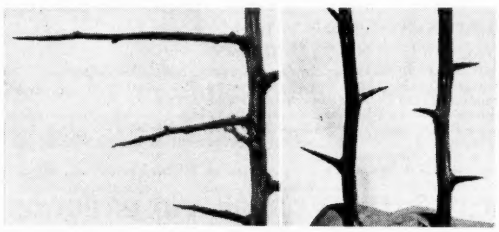
The patient was not ready to start mobilising the finger until March 4. By May 15 he could bring the index fingertip to within a centimetre of the base of the thenar eminence, and he was encouraged to return to work. He improved further during the next 10 weeks and was discharged.

This case is fairly typical. Some of our other patients, with more superficial injuries, required a shorter course of treatment, especially if referred to us early. The swabs revealed penicillin-resistant *Staphylococcus aureus* in three patients and penicillin-sensitive *Staph. aureus* in two; no other pathogen was isolated. One of our patients did not get antitetanus prophylaxis and developed tetanus of moderate severity. This might have happened after any penetrating wound sustained on a farm. None of the ten patients showed signs of bone infection or "bone tumour".

The patient described in the case-report twice collected blackthorns for us and delivered them in a sterile package; he obtained the specimens from the place where he sustained his injury. These thorns were cultured. The first specimen yielded an aspergillus, but saprophytic mycobacteria or actinomyces were not isolated. Subcultures of the second specimen yielded only aerobic spore-bearers and micrococci at 22°C and 37°C.

Discussion

Cactus spines, being organic material, can produce a foreign-body granuloma which may require surgical attention (Boyd 1956). Maylan (1952) recorded that certain plant thorns—e.g., rose and yucca—"in or near bone can cause a reaction in this tissue which may simulate a neoplasm or granuloma". Uteau and Bouget (1928) reported that in the Basque country the peasants attribute peculiarly noxious effects to the prick of the thorns of certain shrubs. These authors noted that two acquaintances had tetanus after thorn wounds. Also they held that the fly-infested putrefying bodies of birds and small animals spitted on these thorns by shrikes and other birds stocking their larders accounted for the inflammation after the thorn pricks. They compared these infections to those following an "anatomical prick" in the post-mortem room or the serious finger infections endemic among the cod-fishers of Newfoundland. (Presumably they were referring to "fat finger" or "seal finger", a condition well described by Candolin [1953].) Dr. G. Taylor, director of the Royal Botanic Gardens at Kew, told me that a member of his staff had noted that "shrikes often impale their 'kills' on the thorns of blackthorn and that this might conceivably cause some sort of bacterial infection". Brimble (1949) pointed out that "these thorns easily snap at their tips, which explains why in some rural areas the blackthorn is supposed to be poisonous, because when the thorn penetrates the skin the tip breaks off and becomes embedded in the flesh and festering ensues". Some of the differences between the thorns of the blackthorn and hawthorn are apparent in the figure.



The smooth short needle-sharp spine of the hawthorn (right) is in sharp contrast to the rough long brittle thorn of the blackthorn (left).

We inquired of Dr. J. W. Fairbairn, reader and head of the department of pharmacognosy, University of London, and Dr. W. O. James, F.R.S., professor of botany, Imperial College, London, regarding the "poisonous nature" of these thorns; but neither was aware of any toxic substance that had been isolated from them.

* This work was done while the author had a research grant from the Nuffield Provincial Hospital Trust. Present address: Orthopædic Division, Toronto General Hospital, Toronto, Canada.

Summary and Conclusions

1. In ten blackthorn injuries of the hand the average interval between time of injury and reference to the accident service was 8·7 days, and the average duration of outpatient treatment was 45 days.

2. Sixty other patients with various thorn injuries seen during the same period required outpatient treatment for an average of 12 days.

3. Bacteriological examination of these blackthorn wounds revealed penicillin-resistant staphylococci in three patients and penicillin-sensitive staphylococci in two; no other pathogens were isolated. One patient developed tetanus of moderate severity. Cultures of blackthorns obtained from hedges yielded no specific pathogen. Histological examination showed a non-specific granulomatous reaction.

I am grateful to Mr. J. C. Scott, director of the accident service, for his interest and help; to the members of the bacteriology department and in particular to Dr. R. L. Vollum, bacteriologist to the United Oxford Hospitals; to Dr. R. H. Cowdell, pathologist to the United Oxford Hospitals; to Mr. B. Juniper, of the School of Botany, University of Oxford; and to Mr. E. Tugwell of the photographic department, Radcliffe Infirmary.

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CATHETER DRAINAGE AND INFECTION IN ACUTE RETENTION OF URINE

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IN a previous investigation of postoperative urinary infection, it was found that about a third of the patients who came for operations on prostate or bladder were already infected (Miller et al. 1958). Most of these infected cases had been catheterised immediately after emergency admission with acute retention of urine. Many of the organisms were resistant to antibiotics, which indicated that they originated in the hospital and that in all probability the patients had acquired the infection as a result of catheter drainage, having entered the hospital with sterile urine. Air bubbles which ascended in the drainage tube were found to carry bacteria to the bladder and to constitute an important cause of infection.

In the same investigation, it was shown that the use of closed aseptic bladder drainage reduced infection after prostate operations, and so it seemed obvious that the same principle could be applied to bladder drainage in cases of acute retention of urine. In such patients, bleeding is ordinarily no problem so that no provision is needed for washing out the bladder.

Methods

In 1957 a simple closed-drainage apparatus was introduced which could be sterilised and kept ready for use in the wards. It was then used in a controlled trial on patients with acute retention of urine who were admitted as emergencies to the Bristol Royal Infirmary from February, 1958, to April, 1959, and to Southmead Hospital from October, 1958, to April, 1959. Altogether, 118 patients with acute retention were treated by continuous bladder drainage; 100 had sterile urine initially and these were the subjects of our investigation. Most of them came to operation after periods of drainage varying from one day to several weeks, but a few were discharged without operation. For practical reasons a completely random choice of admissions could not be made, so patients admitted under the care of some surgeons were catheterised and connected to an open-drainage system, while the remainder had the special closed-drainage system connected.

For open drainage, a piece of boiled rubber tubing three feet long was attached by a sterile glass connection to the catheter with the free end hanging over the side of the bed into an open bucket or urine bottle. The closed-drainage apparatus (fig. 1) consisted of a Winchester bottle (2-litre capacity) through the rubber stopper of which two holes were bored. A glass tube through one hole dipped below the surface of 100 ml. of liq. formaldehyde *B.P.C.* in the bottom of the bottle. The other hole was left as an air outlet. The glass tube with the rubber stopper was boiled for three minutes before assembling the apparatus. The formalin served not only to sterilise the inside of the clean bottle by the overnight action of its vapour, but also as a disinfectant air trap to prevent any bacteria which might enter through the air outlet from reaching the drainage tube alive, and also to prevent the passage of air bubbles up the tube. A tablet of paraformaldehyde (' Formagene ') was placed on the top of the stopper, which was then covered with a ' Cellophane ' bag to maintain the sterility of the upper end of the tube prior to use. For fluid-balance records, a printed volume scale was attached to the outside of the bottle. For use the cellophane bag was removed and, with aseptic precautions, the catheter was connected to the glass inlet tube of the bottle by means of a boiled rubber tube. When a bottle became full, it was replaced, with careful asepsis, which included clamping the tube near its lower end to prevent the ascent of air bubbles. Urine was taken for examination when the catheter was first inserted, and afterwards daily by means of a sterile needle inserted into the tube, as previously described.

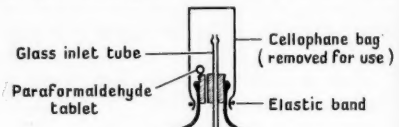


Fig. 1—Apparatus for closed aseptic drainage of the bladder, when irrigation is not required.

The bacteriological methods and the diagnostic criteria of infection were the same as before.

Results

Of the 100 patients admitted with sterile urine, 15 were excluded from the trial for the following reasons: (*a*) 7 either had an operation performed or died within twenty-four hours of admission; (*b*) 4 had prophylactic antibiotics; or (*c*) 4 required repeated catheterisation during the first few days (and all became grossly infected during this time).

Of the remaining 85 patients, 26 were treated with open drainage and 49 with closed drainage, while in a further 10 who started with closed drainage asepsis was broken by the

TABLE I—INCIDENCE OF URINARY INFECTION IN PATIENTS WITH ACUTE RETENTION OF URINE, TREATED BY OPEN BLADDER DRAINAGE AND BY CLOSED ASEPTIC DRAINAGE

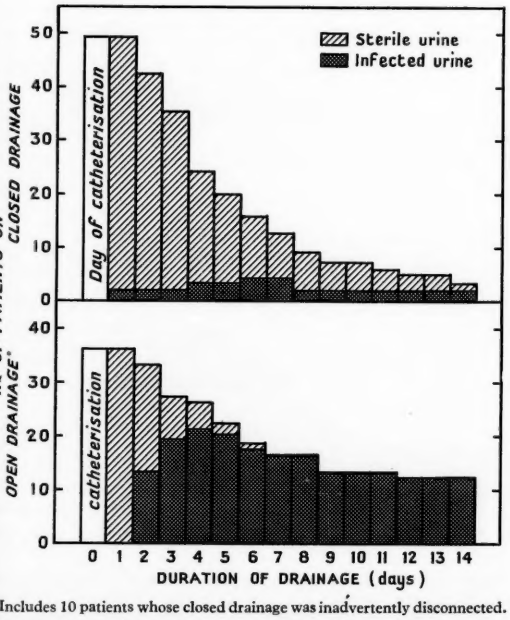
Drainage	Patients	
	Total	Infected
Open	26	19 (73%)
Closed	49	5 (10%)*
Closed but disconnected	10	9 (90%)

* 2 of these patients became infected within eighteen hours of inserting the catheter, probably as a result of the catheterisation and not of subsequent retrograde infection.

disconnection of the drainage tube which was then temporarily blocked by a wooden spigot for such reasons as visits to X-ray department, bathing, and getting up to sit in a chair. The nursing staff did not appreciate at first that the closed-drainage system, once established, must never be disconnected, but since the startling incidence of infection in these cases has been observed there has been no difficulty in maintaining the closed system. Table I shows the incidence of infection, by organisms other than *Staphylococcus albus*, during continuous drainage in this group of 85 patients. The high infection-rate (9 out of 10) in patients who had their closed-drainage system disconnected is notable and emphasises the danger of acquiring infection from spigots, blankets, pyjamas, &c.

Time of Onset of Infection

On open drainage infection usually developed quickly, whilst on closed drainage survival without infection was the rule even when the drainage was continued for many days (fig. 2). Of the 5 patients on closed drainage who did become infected, 2 developed their infections within eighteen hours of catheterisation, probably as a result of the insertion of the catheter and not of subsequent retrograde infection. None of the 10 patients whose closed drainage was inadvertently disconnected survived infection for more than two days afterwards.


Sterile urine
Infected urine
Day of catheterisation
catheterisation
NO. OF PATIENTS ON CLOSED DRAINAGE
NO. OF PATIENTS ON OPEN DRAINAGE*
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
DURATION OF DRAINAGE (days)

* Includes 10 patients whose closed drainage was inadvertently disconnected.

Fig. 2—Urinary infection following insertion of indwelling catheters, in relation to method of draining the bladder.

Nature of Infection

In our hospitals, most urinary infections after prostate operations are caused by "hospital organisms" with abnormal antibiotic sensitivities (Gillespie 1956). Similar organisms caused infection in the cases described above (see table II).

Discussion

In all catheter drainage systems, after the initial catheterisation has been achieved without infection the chief dangers are contamination of the end of the catheter by disconnection, and by bacteria conveyed by air bubbles which rise up the drainage tube from the open end. This latter hazard can be avoided by using a closed system with an antiseptic fluid seal in the collecting bottle.

TABLE II—ANTIBIOTIC RESISTANCE OF BACTERIA IN INFECTIONS COMPLICATING CATHETER DRAINAGE OF ACUTE RETENTION OF URINE

Organisms	Total infections	Antibiotic sensitivities
Streptococcus fæcalis ..	7	..
Staph. aureus	6	1 sensitive and 5 resistant to penicillin. 4 also resistant to sulphonamides, streptomycin, and other antibiotics
Coliform bacilli ..	8	All resistant to sulphonamides and streptomycin
Proteus species ..	10	All resistant to sulphonamides and streptomycin. 9 also resistant to other antibiotics
Pseudomonas pyocyanea	2	1 sensitive and 1 resistant to sulphonamides, streptomycin, chloramphenicol, and oxytetracycline
Other gram-negative bacilli	4	All resistant to sulphonamides, streptomycin, and oxytetracycline
Total	37	28 organisms with abnormal antibiotic resistance

Infections by *Staph. albus* are not included.

So many complications of prostate operations are due to infection that every effort should be made to prevent infection both before and after operation. Bacteria which are allowed to invade the urinary tract are potential causes of lethal bacteræmic shock, septicæmia, or pyelonephritis (Ezzo and Knight 1957, Slade 1958, Miller et al. 1958). In recent years, emergency prostatectomy has been advocated as the best treatment for acute retention because it avoids preliminary catheter drainage with its inevitable risk of infection. In our experience emergency prostatectomy for acute retention can produce excellent results because of the sterile operation field which can be maintained, but there is also little doubt that if one can avoid infection by other means and so enable the operation to be done at a reasonable hour with the same chance of maintaining sterile urine, one may also avoid other hazards incidental to emergency surgery performed at a late hour of night. The ease with which these cases become infected is demonstrated by the results in the group in which the catheter was disconnected. To be effective, therefore, the drainage system must be kept closed for the whole period of drainage.

The same system could be used for continuous drainage of the bladder in other conditions.

Summary

A controlled trial of a simple closed aseptic drainage apparatus for use after catheterisation for acute retention of urine is described.

The apparatus can be cleaned, sterilised, and kept ready for use in the ward.

Its use in the treatment of patients with acute retention of urine enabled sterility of the urine to be maintained in the great majority of cases, until they came to operation. With open drainage, most patients quickly became infected.

We thank the board of governors of the United Bristol Hospitals and the management committee of Southmead General Hospital for grants towards the cost of this research, and the ward sisters for their enthusiastic assistance.

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Slade, N. (1958) *Proc. R. Soc. Med.* **51**, 331.

THE DIURETIC EFFECT OF SPIROLACTONE SC-9420 IN A CASE OF SECONDARY ALDOSTERONISM

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Kagawa et al. (1957) and Liddle et al. (1957) reported that synthetic steroids—the spirolactones designated SC-5233 and SC-8109—block the renal effects of aldosterone and deoxycortone (desoxycorticosterone) in adrenalectomised animals and patients with adrenal insufficiency. In the absence of sodium-retaining hormones the drug had no effect.

The magnitude of the response was directly related to the dose of steroidal spirolactone and inversely related to the dose of sodium-retaining substances given. Therefore the blocking effect was thought to result from competitive inhibition, probably at the level of the renal tubules.

When a high urinary output of aldosterone was induced in normal subjects by feeding a low-sodium diet, spirolactones had the same effect as in patients with Addison's disease who were receiving deoxycortone. The drugs were also given to a number of patients with œdema due to congestive heart-failure, who, as was observed by Deming and Luetscher (1950), excrete large amounts of sodium-retaining substances in the urine. Most cases responded with increase in sodium and water excretion and no change or reduction in the excretion of potassium. The observed reduction in the excretion of titratable acid and ammonia is regarded as further evidence that steroidal spirolactones act as specific aldosterone inhibitors (Liddle 1958).

Kerr et al. (1958) gave SC-8109 by intramuscular injection to three patients with liver cirrhosis and ascites. A sodium and water diuresis occurred in two; potassium output and body-weight did not change.

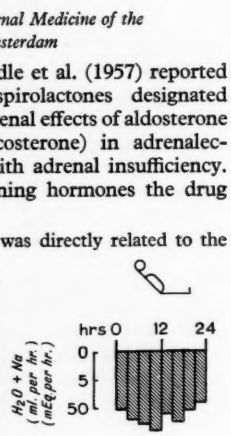

Fig. 2—Diurnal excretory rhythm. Experimental conditions as described under fig. 3. Sodium output was less than 1 mEq. per day, too small to be depicted. Both results of duplicate determinations of aldosterone are given.

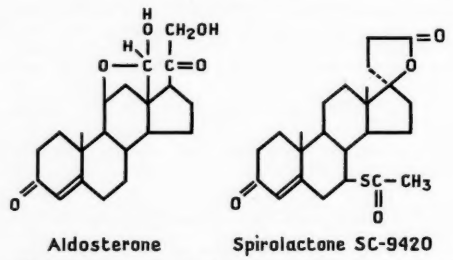

Fig. 1—Chemical formulæ of aldosterone and the steroidal spirolactone SC-9420.

Unfortunately these spirolactones have to be given parenterally in microcrystalline suspensions or oily solutions, the effective oral dose being 30–60 times the parenteral dose.

We have used a new spirolactone SC-9420 (fig. 1) on which no clinical data have hitherto been available. It

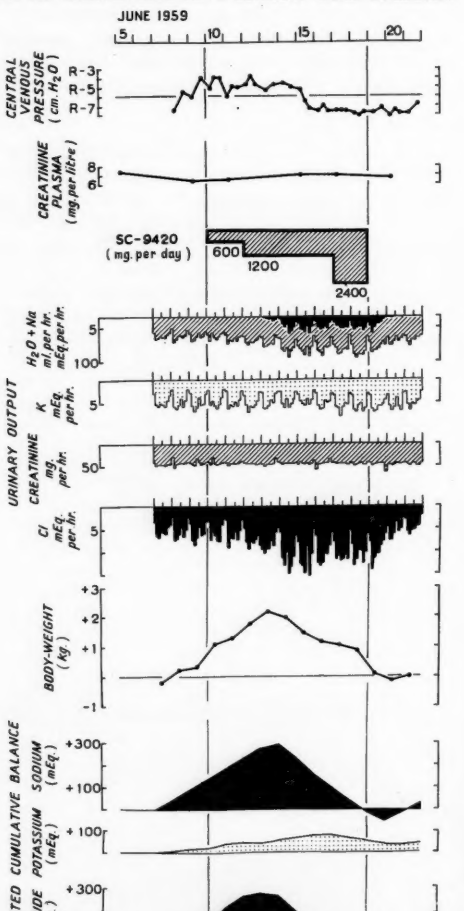

Fig. 3—Effect of SC-9420. During the observation period the patient remained in bed and received 3-hourly equal supplies of food providing 1710 calories, 57 mEq. Na, and 85 mEq. K daily, and drugs making a total of 30 g. urea, 48 mEq. KCl, 64 mEq. NH_4Cl, 0·4 mg. digoxine, 16 mg. thyroid, and 4 μg. triiodothyronine daily.

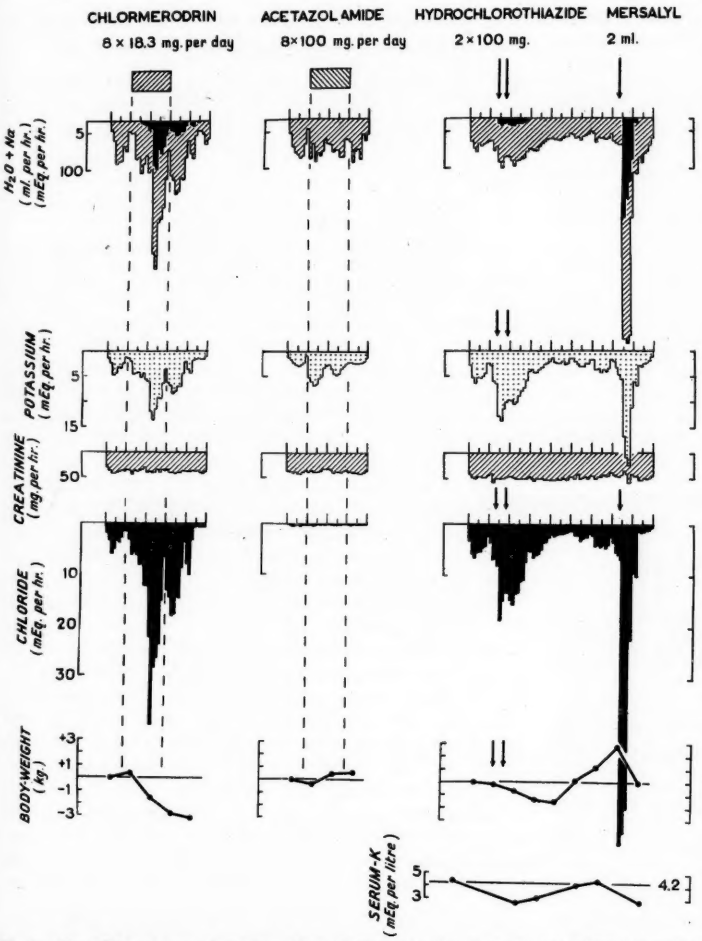

Fig. 4—The effect of four diuretics. Same legend as in fig. 2. $CaCl_2$ was given instead of NH_4Cl during the treatment with chlormerodrin, and no KCl and NH_4Cl was given during the treatment with acetazolamide.

can be given by mouth. The makers claim that its dose-response relation is better than that of the earlier spirolactones. We tested it in a proven case of secondary aldosteronism and compared the pattern of diuresis with that induced by other diuretics.

Investigation

The patient, a highly cooperative man of 29, has severe chronic heart-failure due to rheumatic mitral stenosis and incompetence with auricular fibrillation.

Previous History

He has been under our close observation for 6 years. Treatment has been by a salt-free diet, digoxin, and mersalyl, with sufficient amounts of ammonium chloride; several times urea has had to be administered for many weeks to combat hyponatræmia. Gradual deterioration of cardiac function led in 1953 to inefficacy of even large doses of mersalyl. This necessitated a total suppression of thyroid function with ^{131}I, after which the mersalyl became effective again. He is on a subliminal supply of thyroid powder, and his intake of salt and water is rigidly restricted. Moreover, he still needs ammonium chloride and injections of mersalyl to keep him free from œdema. For 6 years he has not excreted any sodium except on the days that mercurial diuretics were given. Renal function is unimpaired. On rigid fluid restriction urine osmolarity rises to 1200 milliosmol per litre. Creatinine-clearance is about 120 ml. per minute (more than 50 determinations).

Unfortunately increasing symptoms of hypersensitivity to mersalyl have developed. We have therefore tried the effect of other diuretics on water and electrolyte excretion under the rigorously standardised conditions described in previous papers (Borst and de Vries 1950, Borst 1954).

Observations without Spirolactone

The patient was kept in bed on an intake of 57 mEq. daily. The urine was collected in 3-hour periods and analysed for sodium, chloride, potassium, and creatinine. Under these conditions even small changes in the pattern of diuresis can be distinguished. Body-weight and arterial and central venous pressure (method of Borst and Molhuysen 1952) were recorded daily; serum electrolytes, hæmoglobin, and plasma creatinine at regular intervals. A corrected cumulative balance of sodium, potassium, and chloride was calculated as described by Molhuysen et al. (1950).

Using the method of Moolenaar (1957, 1958) we found a urinary excretion of 205-310 microgrammes aldosterone per day, whereas the normal values for persons on a normal salt intake are 3–13 microgrammes. During one of the experiments the patient excreted on a control day more aldosterone in a 3-hour period than normal persons excrete during the day. The highest aldosterone output was between midnight and noon (fig. 2).

Effects of Spirolactone

Fig. 3 shows that in the control period no sodium was excreted. The cumulative sodium balance was positive, and the body-weight and central venous pressure rose. After the dosage of spirolactone had been increased to 1200 mg. per day sodium output started, and it is noteworthy that the excretion pattern of sodium followed the normal diurnal rhythm. The cumulative sodium balance changed from about +300 mEq. to zero. Chloride output had the same pattern. The influence on the potassium excretion was insignificant. However in the period when the sodium balance was negative the (corrected) cumulatice potassium balance showed a slight positive trend. The excretion of creatinine and the creatinine-clearance were unaffected. Increasing the dose of SC–9420 to 2400 mg. per day for 2 days had no additional effect.

With the small supply of SC–9420 available the treatment could not be continued. After it was abruptly stopped the sodium output took at leat 36 hours to return to the zero level.

The levels of serum electrolytes remained constant during the experiment; nor did the arterial pressure and pulse-rate change. The body-weight and the central venous pressure rose and fell parallel with the sodium balance. At the peak of retention the patient was uncomfortable and dyspnœic, and he benefited greatly from the diuretic effect of the spirolactone. The only side-effect noted was slight drowsiness.

The excretion pattern of aldosterone and other adrenocortical steroids during the trial with SC-9420 could not be studied, because immediately after the beginning of the treatment at least two oxidation products of the steroidal spirolactone were excreted in the urine and interfered with the chromatographic separation of aldosterone and the Zimmermann colour reaction.

Fig. 4 shows the renal response to several diuretics in the same patient under similar conditions. It is clear that the effect of spirolactone SC-9420 differs from that of the diuretics quantitatively and qualitatively.

Mersalyl provoked a large diuresis comprising water, sodium, chlorides, and potassium: the effect started at once and lasted 24 hours. Chlormerodrin, a mercury compound for oral use, showed the same pattern but the effect lasted longer. The only effect of acetazolamide (' Diamox ') was an increased excretion of potassium. Hydrochlorothiazide in high dosage gave a small sodium output, yet the sodium balance remained positive. There was a very marked rise in the excretion of potassium. In spite of the 85 mEq. potassium in the diet and the additional supply of 48 mEq. potassium per day, the cumulative potassium balance became negative (balances not presented in fig. 4) and the serum-potassium level dropped from 4·3 to 2·75 mEq. per litre. The diuresis was followed by a compensatory retention of potassium.

Although the diuretic effect of SC-9420 is weaker than that of mersalyl, the results obtained in a short experiment suggest that the spirolactone by " selective chemical adrenalectomy " can also keep this patient in circulatory and electrolyte equilibrium, which non-mercurial diuretics could not achieve.

Summary

The new spirolactone SC-9420 was tested under standardised conditions in a patient with heart-failure, who excreted large amounts of aldosterone in his urine and who for 6 years had not excreted sodium in the urine except when mercurial diuretics were given. The spirolactone induced an appreciable sodium output, while the potassium output remained almost constant. The characteristic excretion pattern could be distinguished from that produced with various other diuretics in the same patient. Side-effects were unimportant.

SC-9420 used in this trial was supplied by Messrs. G. D. Searle. We thank Prof. A. Querido (Leiden) for his instructions and help with the aldosterone determinations.

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" . . . On admission he had been asked if his diet was normal and had replied yes. After some time one of the physicians asked what exactly had he been eating, and when this question was put, the patient said he had been eating little more than bread, margarine and treacle during the last three years. In asking the patient if his diet was normal, the questioner had wanted to know if his diet was suitable to maintain health; in saying that his diet was normal the patient had wanted to say that there had been no recent change from his usual diet. This is an example where the questioner failed to obtain the information he required because different people attributed alternative meanings to the same word."—M. L. JOHNSON ABERCROMBIE, *The Anatomy of Judgment*, p. 106. London: Hutchinson. 1960.

THE NATRIURETIC ACTION OF HEPARIN AND SOME RELATED SUBSTANCES *

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IN an earlier paper (Majoor et al. 1957) we showed that heparin has a diuretic action in patients with œdema of varied ætiology. Moreover, in a man with coronary insufficiency without œdema or any other signs of heart-failure, sodium balance became distinctly negative and potassium balance slightly positive during intravenous heparin therapy. The diuretic effect never appeared until after 36 hours of treatment, and did not reach a maximum until 3 days later. When the heparin injections were discontinued, sodium excretion took about two days to return to its basal level. In one patient potassium excretion was found to be increased in the first few days after stopping the drug. The combination of natriuresis and potassium retention suggested that heparin might suppress the adrenal cortical function.

Coumarin drugs did not increase sodium excretion in any of these patients.

Since 1957 we have accumulated further evidence that heparin is a diuretic with a characteristic excretion pattern for sodium, often accompanied by slight potassium retention, and that it acts both in patients with œdema and in healthy persons (Majoor et al. 1960). In this paper we report on the diuretic activity of the semisynthetic heparin congeners ' Thrombocid '† and Ro1-8307.‡ Thrombocid is an anticoagulant used in many German clinics. Ro1-8307 is a heparinoid said to have low anticoagulant activity with relatively distinct clearing properties (Studer et al. 1956, Reber et al. 1959). Table I

* We are indebted to the Organisation for Health Research, T.N.O., for a grant in support of this investigation.
† Manufactured by Dr. Benend K.G., München-Solln, Germany.
‡ Ro1-8307, nr. 36, was supplied by the Hoffmann-La Roche Laboratories. Basle. The drug is not yet commercially available.

TABLE I—CHEMICAL AND PHYSIOLOGICAL PROPERTIES OF HEPARIN, RO1-8307, AND THROMBOCID

—	Heparin	Ro1-8307	Thrombocid*
Chemical composition	Mixture of mucoitin polysulphates	N-formyl-chitosan polysulphuric acid	Xylan-poly-sulphuric acid
Source	Extracted from lungs or livers	Semisynthetic product of animal origin	Semisynthetic product of vegetable origin
Molecular weight ..	12,000–20,000	Approximately 5000	Approximately 3000
Sulphur content ..	10–14%	Approximately 15%	Approximately 14%
Carbohydrate part of molecule	Glucosamine and glucuronic acid	Acetyl-glucosamine	Xylose
Anticoagulant effect..	+++	In humans far lower than heparin (on a weight basis)	40–45% of heparin (on a weight basis)
Clearing effect ..	+++	About 10% of heparin in humans. About 12% of heparin in rabbits	++
Diuretic effect ..	+++	++	++
Daily dose necessary for diuretic action	200–400 mg.	400–800 mg.	600–800 mg.

* Details communicated by manufacturer.

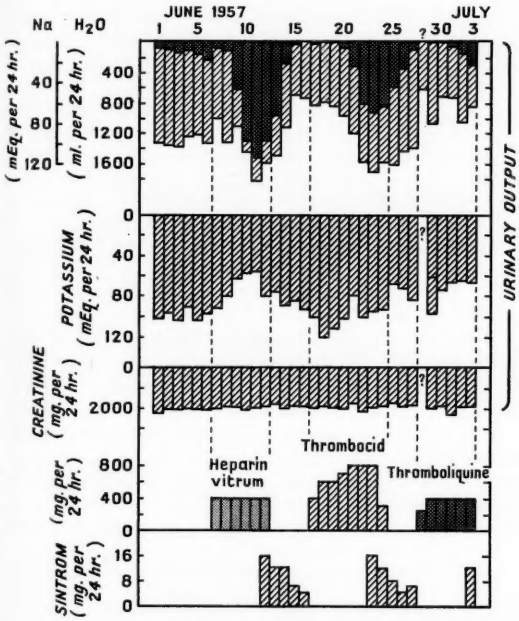

Fig. 1—Diuretic response to two commercially available heparins and thrombocid in patient A.

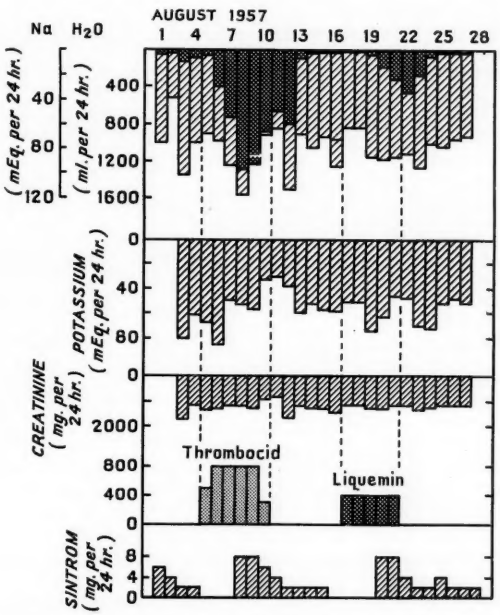

Fig. 2—Diuretic response to thrombocid and the heparin liquemin in patient B.

shows some chemical and physiological properties of the three polysaccharide sulphates used.

Material and Methods

The diuretic action of heparin and the two heparinoids was studied in six patients—three with thrombosis of the legs, one with thrombosis of the brachial vein, one convalescent from bronchopneumonia, and one with a nephrotic syndrome. Three or four intravenous injections were given each day, for 5–8 days in most patients. The daily dose for patients A, B, D, and E is indicated in the figs. 1–4. C and F received 300 mg. of heparin daily for 4–6 days. During a second period of investigation increasing amounts of Ro1-8307 were given (100–450 mg. daily) to a total of 3000 mg. over 15 consecutive days in patient C and 3000 mg. over 8 days in patient F.

As heparin and heparinoids are sodium salts of strong acids, we have determined the sodium content of the preparations used. We found 0·27–0·31 mEq. Na^+ per ml. for all three drugs (1 ml. contains 50 mg. of the drug). Daily sodium intake was increased in this way with 1·5–2·0 mEq. per 24 hours during heparin or Ro1-8307 therapy. As thrombocid was given in doses up to 800 mg. per 24 hours, these patients received a sodium increment of at most 5 mEq. per 24 hours. It is clear from figs. 1–4 and table II that these small amounts of sodium could not be the cause of the enhanced sodium output found in our patients.

Diets

Two kinds of diets were supplied to the patients:

(*a*) The 24 hours were divided into eight periods. At the beginning of each 3-hour period the patients drank a constant amount of milk and water, in most experiments supplemented by a fixed quantity of canned fruit-juice of one consignment, some biscuits, and in some cases a few grammes of cheese, always of the same lot. In this way the intake of fluid, electrolytes, and calories was kept constant. At the end of each period urine was collected and great care was taken to avoid loss. During the observation the patients remained recumbent. This technique of examination was described by Borst and de Vries (1950).

(*b*) All foods and drinks were weighed and measured, and the daily ration was kept constant. The sodium content of these diets was low (about 10–20 mEq. per 24 hours). To keep the potassium intake constant, canned vegetables of one kind and the same brand were used. Three meals were given each day. Urine was collected over 24-hour periods. All patients were weighed daily before breakfast.

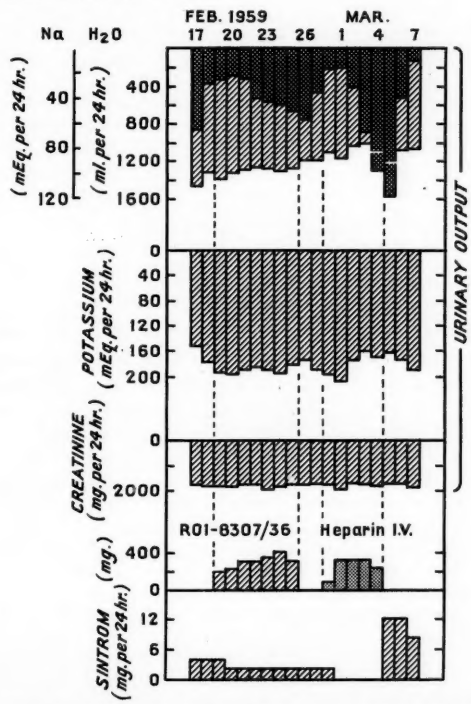

Fig. 3—Diuretic response to Ro1-8307/36 and heparin in patient D.

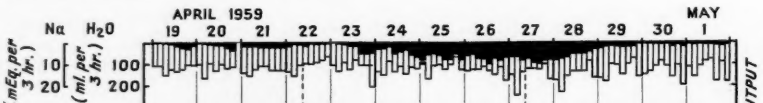
APRIL 1959
MAY
19 20 21 22 23 24 25 26 27 28 29 30 1
Na
H2O
(mEq. per 3 hr.)
(ml. per 3 hr.)
K+ (mEq. per 3 hr.)
CREATININE (mg. per 3 hr.)
URINARY OUTPUT
R01-8307/36 100 mg. per 6 hr.

Fig. 4—Diuretic response to Ro1-8307/36 in patient E.

Laboratory Methods

Sodium and potassium were determined by flame photometer. To check the accuracy of urine collections creatinine was determined in all samples, using the alkaline picrate method. For purposes of comparison the mean daily urinary excretion of water, sodium, potassium, and creatinine was calculated over short periods before, during, and after administration of the drug used. To represent the period of treatment, the days with a maximal urinary sodium output were selected: in most cases this was the 3rd to 5th day of drug administration. To represent the period after drug administration, we chose the first days when pre-treatment levels of sodium excretion were regained—often the 3rd to 5th day after withholding heparin or heparinoids.

Results are shown in table II and the figs. 1–4.

Results

All patients responded to heparin or heparinoids by an increase of urinary sodium excretion. The pattern of this response is seen in figs. 1–4. Sodium excretion did not increase until after 36 hours of therapy, and was maximal after 3–5 days. At the same time potassium excretion decreased slightly or remained constant. For 2–3 days after withdrawal of the drugs a slight increase in potassium excretion was noted in some cases, usually associated with a urinary sodium output lower than it was before treatment.

Compared on a weight basis, thrombocid and Ro1-8307 seem to be less potent diuretics than heparin.

Discussion

As most of these results were obtained in patients with thrombosis, the natriuretic action of heparin might seem attributable to improvement of the circulation, caused by the action of heparin on the thrombotic process and the absorption of local œdema. Against this explanation are the following facts:

1. Coumarin drugs did not increase sodium excretion in any of our patients.

2. Heparin had a distinct effect on sodium excretion in patients E and F who had no thrombosis.

3. Ro1-8307 has almost no influence on coagulation, but shares the natriuretic properties of heparin.

4. During heparin therapy, slight retention of potassium was seen in most patients. Borst (1954) has shown that circulatory diuresis is usually attended by potassium excretion.

A diuretic pattern consisting in elimination of fairly large amounts of sodium (and chloride) with moderate amounts of water, and retention of potassium, points to the distal renal tubules as the site of action. This excretion pattern is similar to that found in Addison's disease and can be reproduced by administration of amphenone (Renold et al. 1957, Thorn et al. 1957) and spirolactones (Liddle 1957). Hence it seems possible that heparin and the heparinoids (or their metabolites?) act by reducing the output of aldosterone, as amphenone does; by blocking steroid action in the kidney, as suggested for the spirolactones; or by accelerating the destruction or

TABLE II—MEAN URINARY EXCRETION OF WATER, SODIUM, POTASSIUM, AND CREATININE BEFORE, DURING, AND AFTER TREATMENT WITH HEPARIN OR HEPARINOIDS

Patient	Sex and age	Clinical diagnosis	Œdema before treatment	Type of diet	Treatment	Body-weight (kg.)		Days' observation*			Mean urine vol. in period mentioned (ml. per 24 hr.)			Mean sodium excretion (mEq. per 24 hr.)			Mean potassium excretion (mEq. per 24 hr.)			Mean creatinine excretion (mg. per 24 hr.)		
						Before treatment	After treatment	Before	During	After	Before	During	After	Before	During	After	Before	During	After	Before	During	After
A	M 34	Phlebothrombosis of right leg	Trace	b	Heparin	78·9	75·9	3	3	3	1260	1460	770	13	87	2	98	59	93	2040	2020	1930
				b	Thrombocid	75·6	75·0	3	3	2	770	1650	1260	2	66	6	93	97	91	1930	1990	1890
				b	Heparin	74·4	73·8	2	2	..	1260	980	..	6	20	..	91	67	..	1890	1870	..
B	F 52	Thrombophlebitis of left leg. Coronary insufficiency without heart-failure. Hypostatic œdema of both legs	None	b	Thrombocid	99·2	96·8	3	5	3	1080	1200	1090	7	73	2	70	43	57	1490	1260	1420
				b	Heparin	96·0	95·0	3	3	4	1090	1160	1000	2	24	3	57	53	57	1420	1280	1240
C	M 17	Phlebothrombosis of left brachial vein possibly of traumatic origin	None	a	Heparin	59·9	58·1	2·5	3	2	1640	1810	1730	28	86	28	84	78	87	1600	1660	1550
				b	Ro1-8307	58·7	58·3	3	3	..	1620	1560	..	2	16	..	32	33	..	1530	1580	..
D	M 46	Spontaneous phlebothrombosis of both legs	Trace	a	Ro1-8307	70·3	70·2	3	3	2	1340	1260	1140	23	51	17	193	184	202	1800	1790	1050
				a	Heparin	70·6	?	2	3	1	1140	1120	1080	17	95	11	202	164	191	1850	1760	1870
E	M 56	Reconvalescent after bronchopneumonia. No œdema	None	a	Ro1-8307	51·0	50·5	3	3	2	920	1030	1030	10	59	11	112	110	110	1170	1150	1080
F	F 22	Nephrotic syndrome, grossly œdematous	+++	b	Heparin	63·7	62·6	3	3	3	840	960	950	4	24	3	83	73	81	1490	1520	1570
				b	Ro1-8307	63·2	61·4	3	3	..	790	930	..	1	24	..	71	81	..	1460	1500	..

* i.e., number of days used for computation of mean outputs.

elimination of aldosterone. These possibilities are being investigated (Cejka et al. 1960).

In sharp contrast to the action of mercurials, acetazolamide, and chlorothiazides, the diuretic action of heparin or the heparinoids never became apparent during the first 36 hours of therapy and never stopped within 48 hours of terminating intravenous administration. Though a late natriuretic response of the same type has sometimes been reported after amphenone and less definitely after spirolactone administration, in other experiments an immediate response was found (Renold et al. 1957, Thorn et al. 1957, Liddle 1957, 1958, Ross and Bethune 1959). As heparin and related substances without exception caused a delayed type of diuresis, at present they seem to occupy a unique position among drugs with diuretic action.

It is interesting that polysaccharide sulphates so different in source, composition, and molecular weight as heparin, thrombocid, and Ro1-8307, should have diuretic actions of about the same magnitude and of exactly the same type. It is possible, too, that the dextran sulphate 'Dexulate' shares this diuretic action, since Jeavons et al. in 1956 observed a patient with venous thrombosis associated with pulmonary embolism, who lost 8·5 kg. in weight during the first 6 days of dexulate treatment. Rapid disappearance of œdema in patients with thrombophlebitis during dexulate administration was also observed by Donzelot et al. (1955).

Our own observations suggest that the natriuretic action of the heparinoid Ro1-8307 deserves further study, because this drug, in the dosage used, is almost devoid of anticoagulant action (Studer et al. 1956, Majoor et al. 1960). Studer et al. (1956) administered Ro1-8307 as a clearing agent to nineteen patients for 8 weeks, without toxic manifestations. But their dose of 100 mg. three times weekly was far lower than that needed for diuretic action.

In the short-term experiments we describe here, with daily doses up to 450 mg., the drug was tolerated without untoward effect by all patients except F—a girl with a nephrotic syndrome who vomited twice on the last day of drug administration. With growing experience with the intravenous and intramuscular administration of Ro1-8307, both in our department and in the department of internal medicine in Amsterdam (Cejka et al. 1960), vomiting and diarrhœa have been noted in only three other patients, all of whom had membranous glomerulonephritis with severe albuminuria. In two of these, who vomited shortly after their first dose of 100 mg. intravenously, treatment was not continued. In the third patient, who was in a remission after prednisone treatment, vomiting and diarrhœa started on the 9th day of therapy, when 4000 mg. of the drug had been given intramuscularly. Toxic manifestations subsided immediately when injections were stopped.

These observations show that a careful watch for drug intolerance should be kept whenever long-term administration of Ro1-8307 in relatively large amounts is used for treating intractable retention of sodium and water.

Summary

The diuretic action of heparin was compared with that of the heparin congeners 'Thrombocid' and Ro1-8307. Each drug produced natriuresis and often slight potassium retention. The renal excretion pattern following administration of these polysaccharide sulphates is very similar to that seen in Addison's disease or after administration of amphenone and spirolactones. This points to their having an inhibitory influence on the secretion or action of aldosterone.

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Preliminary Communication

EFFECT OF HEPARINOID AND SPIROLACTONE ON THE RENAL EXCRETION OF SODIUM AND ALDOSTERONE

Two types of drugs seem to reduce the influence of the adrenal cortex on the function of the renal tubules. Heparin [1] and heparinoids [2] probably act by reducing the secretion of aldosterone by the adrenal. Spirolactones block the effect of aldosterone, deoxycortone, and related substances by competitive inhibition.[3]

We have studied the effect of both types of drugs, given separately and simultaneously, on the urinary output of sodium and aldosterone. This report concerns our first three patients.

PATIENT 1 has cardiac failure with secondary aldosteronism. He was on a strictly standardised diet providing 57 mEq. of sodium daily. Data on the effect of spirolactone are presented in a previous paper.[4] Intravenous injections of heparin (100 mg. four times daily) induced a steep fall in aldosterone output. Sodium excretion started, but was insufficient to induce a negative sodium balance before severe signs and symptoms of congestive failure obliged us to stop the experiment. Moreover, the patient had several large subcutaneous hæmorrhages.

PATIENT 2, a man of 48, with hypertension, was on a salt-poor diet. His weight was constant, while the daily sodium output in his urine ranged from 28 to 10 mEq. (average 17 mEq.). Spirolactone sc-9420, 200 mg. by mouth four times a day, immediately increased the sodium excretion (fig. 1). In the following week urinary sodium output decreased despite continued treatment. Doubling the dosage did not much increase sodium excretion. Owing to the presence of spirolactone metabolites, determination of aldosterone in the urine was impossible. When the determinations could be resumed, the aldosterone output was higher than before treatment. Heparinoid Ro1-8307, 800 mg. given intramuscularly twice daily as a depot, was followed by a fall in aldosterone excretion and by a gradual increase in urinary sodium output. Addition of spirolactone hardly increased the sodium output; nor did addition of 0·5 g. chlorothiazide daily. The patient, however, was by this time in a state of salt depletion, the blood-sodium level having fallen to 128 mEq. per litre.

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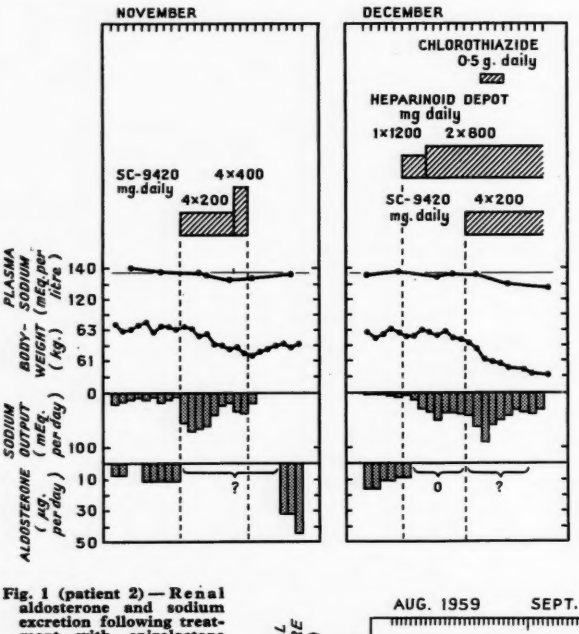

Fig. 1 (patient 2)—Renal aldosterone and sodium excretion following treatment with spirolactone and heparinoid separately and simultaneously.

PATIENT 3, a married woman born in 1902, has had congestive heart-failure since 1952.

In 1955 she was operated upon for concretio pericardii (Professor Boerema, Amsterdam) after which kymography showed an increase in cardiac pulsations but the congestive heart-failure did not improve. For four years she remained in fairly good condition. She was on a salt-poor diet and received 2 ml. mersalyl every fifth day, together with an adequate amount of ammonium chloride. In spite of this regimen, in the spring of 1959, œdema increased and in August she was admitted to the Binnengasthuis. The heart-failure was severe. She had massive œdema and a very high central venous pressure, which amounted to 3 cm. above the level of the sternal angle (see fig. 2).

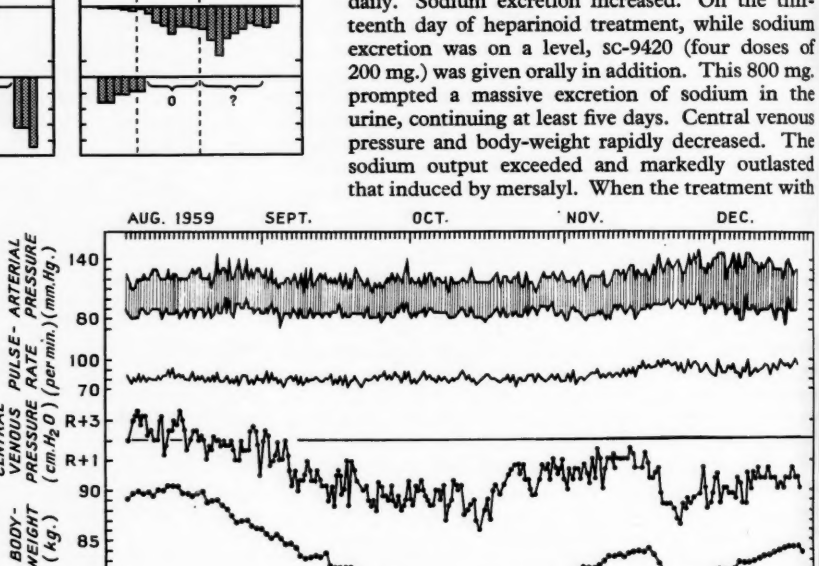

Fig. 2 (patient 3)—Comparison of the natriuretic effect of mersalyl and the chlorothiazides with that of heparinoid and spirolactone administered separately and simultaneously. The blood-sodium level (not presented) was almost constant.

Treatment with salt restriction and diuretics—of which mersalyl had most effect—resulted in a slow decrease of the central venous pressure, but this remained 2–4 cm. above the normal level. The œdema diminished as shown by the loss of body-weight. After the loss of œdema she developed a voracious appetite and could hardly be satisfied with 1900 calories. The intake of salt was 17 mEq. per day. In spite of treatment with 0·5 g. chlorothiazide daily, no sodium was excreted in the urine. Body-weight and central venous pressure gradually increased. In this period the excretion of aldosterone in the urine was 40–60 μg. per day (see fig. 3). During intramuscular injection of Ro1-8307 (at first 100 mg. and later 200 mg. four times a day) the excretion of aldosterone decreased to 4 μg. daily. Sodium excretion increased. On the thirteenth day of heparinoid treatment, while sodium excretion was on a level, sc-9420 (four doses of 200 mg.) was given orally in addition. This 800 mg. prompted a massive excretion of sodium in the urine, continuing at least five days. Central venous pressure and body-weight rapidly decreased. The sodium output exceeded and markedly outlasted that induced by mersalyl. When the treatment with

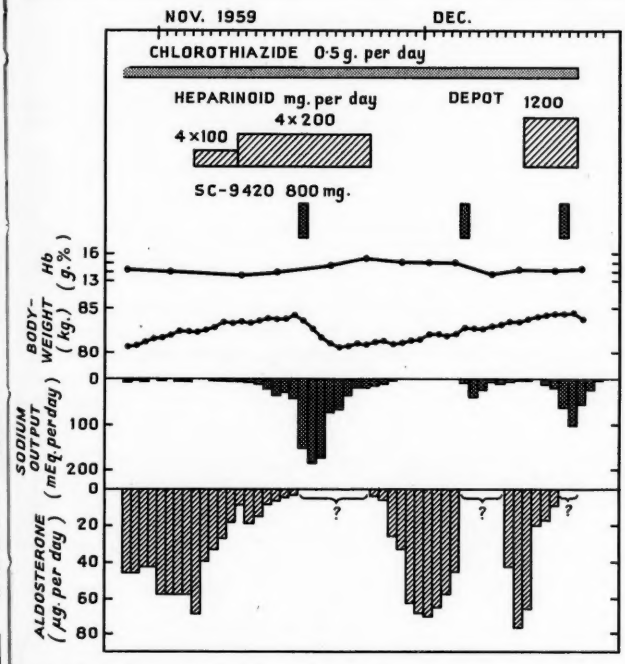

Fig. 3 (patient 3)—Renal aldosterone and sodium excretion following treatment with spirolactone and heparinoid separately and simultaneously.

heparinoids was discontinued, the excretion of aldosterone increased to control levels in four days. Without heparinoid, administration of the same dose of spirolactone for one day resulted in a small excretion of sodium lasting four days. Resumption of heparinoid administration, this time with 1200 mg. of a depot preparation in one intramuscular injection daily, met with the same type of response. Addition of 800 mg. spirolactone again initiated a further appreciable rise in sodium excretion.

The patient left hospital on Dec. 18 in a good condition. She continued collecting the twenty-four hours' urine. That day and the two days thereafter she had no treatment. The last dose of chlorothiazide was given on the 17th at 6 A.M. Nonetheless the sodium output on Dec. 18 was still high and then declined rapidly. The blood-sodium level was almost constant during the whole period of observation, and the creatinine output in the urine fluctuated only insignificantly.

In this case of secondary aldosteronism the effect of the combined treatment with SC-9420 and Ro1-8307 on sodium excretion is much greater than the sum of the effects of the two drugs separately. Though the influence of aldosterone on tubular reabsorption of sodium must have been reduced to a very low level, the peak sodium excretion was much lower than that present in normal persons on a high sodium intake or in some patients with cardiac failure during a good response to digitalis. Therefore we conclude that the sodium retention was caused partly by other factors of the same importance as aldosterone.

The creatinine clearance was slightly higher during the period of greatest sodium excretion but stayed on the same level for some days, during which sodium was again retained. During the second sodium diuresis the clearance was on a lower level. It is highly improbable that sodium excretion in this case was influenced by the alterations in the creatinine clearance.

No side-effects of the heparinoid were noticed; coagulation-time was normal and signs of hæmorrhagic tendency were absent. However, some of the patients with nephrotic œdema, who were treated with the heparinoid Ro1-8307 in the University Hospital at Nijmegen showed signs and symptoms that may be attributed to a toxic effect of the drug.[2]

SUMMARY AND CONCLUSIONS

In three patients on restricted salt intake (two of whom had secondary aldosteronism) administration of heparin and heparinoid Ro1-8307 was followed by a gradual decrease in urinary aldosterone to levels found in normal subjects on an unrestricted salt intake. Sodium output increased, the changes in sodium output not being related to changes in creatinine clearance.

In a patient treated with 1200 mg. heparinoid and 500 mg. chlorothiazide daily, 800 mg. of spirolactone given on one day increased the sodium output for five days, the effect being far more than additive. The sodium output greatly surpassed that induced by mersalyl and the chlorothiazides in high dosage. On the other hand, it was less than that seen in normal persons on a high sodium diet.

Ro1-8307 was supplied by Hoffmann-La Roche Laboratories, Basle, and SC-9420 by G. D. Searle & Co., Chicago.

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Medical Societies

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

Evolution of Viruses

A MEETING was held in London on Jan. 21.

Prof. C. D. DARLINGTON said that a change of host (as in myxomatosis when introduced into Australian rabbits, or measles when introduced into Polynesia) often means an increase of virulence—after which there is a sharp decline both in the virulence of the parasite and in the susceptibility of the host, apparently through natural selection. Transplantation by an arthropod vector can transform the character of a virus, and the question arises whether the vector finds the virus ready-made as an infectious organism. A nucleoprotein propagating itself normally in one organism may become a virus in another: something transmitted by the cytoplasm in heredity, or generated by the cell, becomes communicable by infection. On the other hand a virus can become a harmless nucleoprotein or become latent, doing no harm to its host. Latency is imagined to have existed in all situations where a new virus has arisen where no virus was known before.

Mr. P. F. MATTINGLY pointed out that though each virus is isolated in the tissues of the host, it has like other organisms an ecology of its own, independent of adventitious transfer to man or occurrence in atypical hosts or vectors. At present the

requirements for establishing a mosquito-borne virus are warm-blooded vertebrates, angiospermous plants, and blood-sucking mosquitoes. The first two evolved together in the Tertiary period, and the viruses and mosquito vectors probably evolved with them. The fact that mammalian malaria parasites are transmitted by anophelines, and bird-malaria parasites (in the laboratory and therefore presumably in Nature) by culicines, suggests that anophelines evolved as mammal feeders and culicines (at least in part) as bird feeders. The basic maintenance cycles of mosquito-borne viruses involve culicines only (except for the subgenus kerteszia), and this suggests that the primitive viruses of this group were bird viruses. Aedes-borne viruses are confined to the tropics, culex-borne viruses are found in the subtropics, and tick-borne viruses in the northern steppes. The explanation seems to be that aedes hibernate and æstivate in the egg, and culex hibernate and æstivate as adults, which permits them to withstand the severe conditions of the subtropics. Further north, where only the resistant egg will serve for hibernation, aedes are the dominant mosquitoes; but they do not pass on the viruses through the egg, and are therefore unsuitable for maintaining them, and the mosquito-borne viruses are replaced by tick-borne viruses. The West Nile virus is probably the most primitive of the group-B viruses and the picture would be of invasion from the subtropical savannah northwards to steppes and tick vectors, and southward to tropical habitats and aedes vectors. But possibly the Russian spring-summer viruses are the most primitive, and if this were so the picture might be simpler and more coherent.

Dr. C. E. GORDON SMITH, taking up the evolution of arbor-virus diseases, showed a list of the arboviruses known to cause diseases in man; but he noted that progress may occur from a virus infecting only an arthropod and transmitted through the egg, to a virus transmitted from arthropods to an animal other than man, thence by a second arthropod to man, and finally between man and man through this secondary vector. Hence there may be many arboviruses still " in search of disease ". The factors influencing the maintenance of arboviruses in Nature are extremely complex and are often strongly affected by human activity—e.g., irrigation, insecticides, artificial immunisation, or the effect of sanitation on the age of the population. The viruses themselves fall into several groups, but changes in virulence and antigenic structure, and phase variations, are all observed and are related to mutations. Selection pressures occur in the vertebrate and arthropod hosts.

Dr. C. H. ANDREWES remarked that the viruses are probably very old in evolutionary history; they probably evolved along with their hosts and vectors, and the tick-borne viruses may be the oldest. Their evolution may be affected by short-term factors which are not very fundamental (as in influenza and myxomatosis) or by long-term factors such as those suggested by Mattingly.

Prof. D. S. BERTRAM referred to the fact that virus can pass more easily to the egg in ticks than in mosquitoes, having fewer membranes to cross in the process.

Dr. J. S. PORTERFIELD suggested that there are two time-scales in the evolution of viruses, one of which is short-term and is being witnessed now, as in the development of the Chikungunya virus.

Dr. M. G. R. VARMA, who has worked on the Kyasanur Forest virus, pointed out that, experimentally, mosquito-borne viruses have been propagated in ticks, but not vice versa, which suggests that the tick-borne virus may be the more primitive. Kyasanur virus is related to Russian spring-summer virus, but it is carried by hæmaphysalis and not by ixodes though these are abundant. The Russian virus is transmitted by ixodes.

Dr. P. B. STONES observed that when mosquitoes first evolved there were no mammals, and if viruses then existed they must have been passed from mosquito to mosquito.

Reviews of Books

Forensic Medicine

A. KEITH MANT, M.D., lecturer, department of forensic medicine, Guy's Hospital, London. London: Lloyd-Luke Medical Books. 1959. Pp. 262. 42*s*.

HERE is a well-written concise guide to the points which can be observed and the interpretations which may reasonably be made by general practitioners, police surgeons, and others called to see a body thought to be dead. The book is intended also for those who may have to appraise injuries in the living or the dead, and for those asked to deal with an alleged sexual assault.

When death is unexpected, it is very important that the initial examination of the body and its environment be conducted so that an opinion given at that time is well founded and not just a careless guess; otherwise, as Dr. Mant points out, a family may suffer the early stages of an investigation of a supposed crime, later shown to be a natural death, or a murder may be unsuspected until after necropsy, by which time essential evidence may have been destroyed. All that is described and well illustrated in this book is what may be seen by a careful observer, such as a general practitioner, no special forensic knowledge being required: indeed, all specialised matters, such as necropsies, microscopy, and analyses, are excluded.

What to do, and what not to do, when examining a supposedly dead body is followed by an account of up-to-date methods of estimating the time of death, the " virtual cooling time " method being explained in detail. The characteristics of injuries, applicable to the living as well as the dead body, are dealt with at length, the examination of road accident victims being a useful feature. Guns and gunshot injuries are carefully explained, and much attention is given to various causes of anoxæmia: incidentally, perhaps the only illustration in the book to which exception might be taken is found at the beginning of the chapter on mechanical asphyxia. Infant deaths, abortion, and poisoning conclude the first section of the book.

The second part deals with the medicolegal aspects of sexual offences, and any doctor who proposes to examine the alleged victim or assailant in a supposed sexual assault would be well advised first to study this section in detail, for incomplete physical examinations and incautious opinions based more upon preconceived notions than on fact seriously endanger the liberty or reputation of one of the parties involved. Dr. Mant leaves the reader in no doubt as to the responsibilities of the examining doctor in such cases, but he also offers a comprehensive scheme for a proper examination.

As is apt to happen in a first edition, there are a few trivial points which will doubtless be amended in subsequent editions (e.g., in the legend to fig. 82, reference should be made to fig. 77); but they in no way diminish the considerable value of this realistic work which can be wholeheartedly recommended to all involved in medicolegal affairs. At the very least, Dr. Mant shows the doctor how to avoid the unhappy thought " What on earth am I supposed to see ? "

Antibiotic and Sulphonamide Treatment

A Short Guide for Practitioners. A. R. ANSCOMBE, M.S., F.R.C.S.; D. B. BROWN, M.B., M.M.S.A., M.R.C.O.G.; D. M. DAVIES, M.R.C.P. Editor: M. E. FLOREY, M.D. London: Oxford University Press. 1959. Pp. 150. 10*s*. 6*d*.

THIS little handbook is designed as a brief practical guide to the treatment of infections. It outlines the principal features of the antibiotics and sulphonamides and gives clear instructions for their use and adequate warning about their toxic effects and dangers. It is fully up to date and includes notes on several recently introduced antibiotics.

There can be little doubt that the book well fulfils its limited purpose, and those who want for quick reference a short text dealing only with the practical aspects of these agents will find it an excellent choice.

THE LANCET
LONDON 6 FEBRUARY 1960

The Sign of Babinski

Since BABINSKI [1 2] described the extensor plantar response in man, it has been generally accepted as indicating a disturbance of function in the pyramidal tract. WALSHE [3] concluded that it was an integral part of the flexion reflex in man and was strictly homologous with the nociceptive flexion reflex in animals, described by SHERRINGTON.[4] It has long been known that a transient extensor plantar response may follow an epileptic fit and may appear in biochemical disturbances affecting the nervous system, such as hypoglycæmia; so it is clear that the presence of the sign does not necessarily indicate an anatomical lesion in the pyramidal system. There has been some discussion and indeed criticism [5 6] of the significance of the extensor plantar response as an indication of disturbed pyramidal function, and BRAIN and WILKINSON [7] have lately investigated the response in the human infant, using as stimuli pinprick and cold and, on the sole, key-drag.

They studied 35 children, ranging in age from one day to twenty-seven months. In children up to the age of eight days the responses obtained were almost always extensor and could often be elicited by pinprick or cold as high as the third thoracic segment, but the response was nearly always limited to the side stimulated. The greatest activity of the extensor response was seen in children between five and twenty weeks old, being obtained as a bilateral response to all of the three forms of stimulus applied to the sole; and it could also be obtained bilaterally as a result of stimulating either thigh. Usually a bilateral response could also be obtained from the abdomen and upper chest, but it was definitely or doubtfully flexor almost as often as it was extensor from these levels.

After the age of twenty-one weeks the receptive field shrank progressively from above downwards: only 1 child over the age of twenty-three weeks gave any plantar response to a stimulus above the third thoracic segment, and after the age of nine months there was usually no response to stimulation of the thigh. The response to stimulation of the sole also altered in character; the extensor response became less definite or was replaced by a doubtful or a frank flexor; but, even during the second year of life, the response to a scratch on the sole was not always flexor—sometimes it was a weak flexor, sometimes a weak extensor, and sometimes even a definite extensor. In general cold ceased to be an effective stimulus after the age of twenty-four weeks.

BRAIN and WILKINSON think it probable that the conversion of the infantile extensor response to flexor and the progressive shrinkage of the receptive zone between the ninth and twenty-fourth months of life can be correlated with the progressive myelination of the pyramidal tracts during this period.

BRAIN and WILKINSON also studied the plantar response in 31 children suffering from neurological disease dating from birth or very early in life, including cases of cerebral diplegia, and in 5 adult patients with virtually complete traumatic lesions of the spinal cord in the lower cervical region. In the children cold was rarely effective as a stimulus. A response to pinprick was evoked more easily the nearer the site of stimulus approached the sole; a response was obtained from the third thoracic level in only 4, from the abdomen in 13, from the thigh in 20, and from the sole in all 31. They conclude that the plantar responses of those children with congenital diplegia differ from those of normal infants in whom the pyramidal tracts have not become myelinated. In particular the usual absence of a response to cold and the extent of the receptive field of the reflex correspond more closely to patients with spinal-cord lesions acquired later in life.

LANDAU and CLARE [8] examined the plantar response in 14 normal subjects and 12 patients with consistently extensor responses, using motion pictures and electromyographic recordings. In the normal flexor response the usual pattern included strong contraction of the short hallux flexors, with an associated response in the dorsiflexors of the foot; the extensor hallucis longus was always electrically silent. In the extensor response there was a tonic contraction of the short hallux flexors, contraction of the dorsiflexors of the foot and toes, and a strong contraction of extensor hallucis longus. The essential phenomenon of the extensor reflex is therefore thought to be the recruitment of extensor hallucis longus into contraction alongside the other toe and foot dorsiflexors, with mechanical overpowering of the toe flexors. In studying the changes in the response in several patients who had had acute spinal-cord lesions, LANDAU and CLARE found electromyographic evidence of denervation in extensor hallucis longus and the dorsiflexors of the toes and ankles, and in 1 of these patients an extensor response became flexor in spite of evidence at operation of a virtually complete transection of the spinal cord. They thought that the denervation of the anterior tibial muscles in these patients was due to a lesion of the external popliteal nerve from pressure. In 1943 LEWIN [9] also drew attention to the danger of pressure lesions of the external popliteal nerve in patients with spinal-cord injuries, although he did not study the effect on the plantar response.

These observations of the effect on the plantar response of a peripheral nerve lesion in a patient with severe spinal-cord damage are important and may well explain some of the recorded cases in which the plantar response was flexor in the presence of known damage to the pyramidal tracts. This is not, however, the only cause of flexor responses in spinal-cord lesions. GORDON HOLMES [10] in 1915, studying acute injuries of the spinal cord, recorded a flexion-adduction movement of the toes as the earliest reflex response after a severe cord lesion; this reflex might disappear after a few days and later an extensor response might be found. This observation, confirmed by RIDDOCH,[11] is now well recognised and

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usually indicates a poor prognosis for recovery of spinal-cord function. BRAIN and WILKINSON observe that in 1898 SHERRINGTON had recorded a similar reflex in the monkey after transection of the cord below the level of the brachial enlargement, and that it has also been recorded in the baboon. It seems that when all other spinal-cord functions are abolished there is a rather feeble flexor reflex of the toes in response to a stimulus to the sole, which GORDON HOLMES described as a " unisegmental reflex response in muscles supplied by the first sacral segment ".

The Germ-free Animal

PASTEUR was usually right; but his reasoned guess that mammalian life without bacteria is impossible was proved wrong even in his lifetime. The early attempts to raise germ-free animals were not very successful, but they failed not for lack of understanding of the problem but for minor technical reasons such as improper diets. Today rats, mice, guineapigs, rabbits, and chicks are all raised free from parasites of all sorts, within and without, as a routine procedure which has proved valuable in many kinds of research. Though this is not a cheap hobby for idle moments, the results seem to justify the trouble and expense. A monograph from the New York Academy of Science [1] gives a good idea of the techniques and the results to be expected and will encourage others to try the method.

On the same diets there is not much difference in the development of germ-free and conventional mammals. Analysis of the weights of individual organs shows that heart and brain are of the same size, but the germ-free animal has far less lymphoid tissue. If it is " infected " with a normal fæcal flora, the weight of lymphoid tissue soon reaches that of the conventional animal. If, on the other hand, the conventional animal is fed small regular doses of penicillin from birth, the weight of its lymphoid tissue is not much more than that of the germ-free stock. The development of the lymphoid tissue depends on the stimulus of the intestinal flora. In chicks—as the farmer knows—small doses of penicillin quicken growth; and it has been debated whether this quickening is due to an inhibitory action of the flora of the bowel on growth or to some stimulant action of the antibiotic. The germ-free chick grows at least as fast as the conventional bird fed with penicillin. Of the various species of bacteria in the chicken's bowel which have been fed singly to the germ-free chicks, only *Clostridium welchii* (type A) slows the growth-rate to " normal ". Germ-free mice grow well on a diet lacking some aminoacids essential to the conventional mouse. If they are then given their normal intestinal flora they cease to grow: there is not enough of something for both host and parasite. Was the difference in size of adolescent boys in social classes I and V (which is no longer seen) attributable to some similar deficiency? So striking have been the facts elicited from these germ-free stocks that some biochemists are prepared to say that the science of dietetics must begin again from scratch.

1. *Ann. N.Y. Acad. Sci.* 1959, **78**, 1.

The serum of germ-free mice contains an abnormally large amount of albumin (and for this there is no parallel) but only small amounts of gamma-globulin. It contains complement and properdin but no bacterial agglutinins unless the sterilised food contains dead bacteria. When exposed to an antigenic stimulus, the germ-free animal responds more slowly than the normal. The response to infections is curious and hard to understand. In the normal animal fed by mouth, *Shigella flexneri* is not easy to establish; but in the germ-free animal 9 or 10 organisms introduced by the same route will multiply to 10^9 within eighteen hours. Whereas these will produce no pathological changes, *Bacillus subtilis* causes a rapidly fatal disease; and the same is true of many other bacteria usually looked on as barely pathogenic. Clearly the germ-free animal offers an opportunity to investigate the nature of infections in cavities of the body which ordinarily carry a large mixed flora. We should be able to discover whether *Treponema vincenti* is the " cause " of an ulcerated mouth, or merely a normal inhabitant which takes advantage of existing disease to multiply exceedingly. Many species of bacteria have been blamed for dental decay: here is the possibility of examining their powers in isolation or in combination. Experiments with germ-free guineapigs have shown that, while *Entamœba histolytica* can survive and multiply in the bowel wall, ulceration does not begin until the normal bacterial flora of the bowel is introduced. On the other hand, the germ-free guineapig is susceptible to infection with species of worm whose natural hosts are the mouse or rat and which cannot be established in the normal guineapig.

Though the scope for inquiry is limitless, such research is by no means all easy going. For example, serum hepatitis can be established in one breed of germ-free chicks but not in another. The evidence of the part played by viruses in the production of spontaneous tumours breaks new ground but is hard to interpret. So far, moreover, few of the findings of this technique have had a practical application. The premature infant delivered by cæsarean section and kept in a sterile atmosphere might reach viable size a few days earlier. Almost the same benefit might be derived by feeding it small daily doses of penicillin; but he would be a bold pædiatrician who recommended this regimen. Experience has taught that minor infections do quite a lot to protect us against the major ones. If he was speaking of human life, PASTEUR was after all nearer right than wrong.

The Role of the Stomach in Digestion

THE stomach makes two contributions to digestion: it changes physically and chemically the food put into it and it delivers its contents in a highly regulated manner to the duodenum. The processes of digestion within the stomach and the control of the secretions which contribute to them have been so intensively studied that the dependence of eupepsia on the proper control of gastric emptying tends to be overshadowed. Most medical students are made aware of BEAUMONT's *Experiments and Observations on the Gastric Juice and the Physiology of*

Digestion (1833) and PAVLOV'S *Work of the Digestive Glands* (1916), but in fact digestion within the stomach is probably not essential for normal life. It is usually accepted that the majority of patients with treated addisonian anæmia secrete neither acid [1] nor pepsin,[2] yet they are reported to be at least as healthy as patients of a comparable age [3] and not to be unduly susceptible to diarrhœa or dyspepsia.[4] Although this view about the absence of pepsin in the gastric secretion of patients with addisonian anæmia is acceptable in a general way, some refined studies of gastric proteolytic enzymes by TAYLOR [5] have displayed new features which are too common to be called exceptional. In an extension of earlier work [6] it has been clearly shown that gastric juice from normal persons gives two peak rates of digestion, one at pH 1·6–2·4 and one at pH 3·3–4·0. The activity at low pH is due to the classical pepsin,[7] but the cause of the second peak of activity at pH 3·3–4·0 is more controversial. TAYLOR [8] measured the extent of digestion by the formol titration of carboxyl groups liberated from peptide bonds, and many of the digestion periods were long—three to six hours—by the standards of most other workers. The measurement of carboxyl groups, which are produced in all stages of proteolysis, would be expected to give a different idea of digestion from that obtained by determining the rather special phenolic hydroxyl groups, as, for example, in the popular method of ANSON and MIRSKY.[9] Under TAYLOR'S conditions, with digestion periods usually of the order of three hours, as much as half the proteolysis by human gastric juice can be ascribed to a hitherto almost ignored enzyme acting at pH 3·3–4·0. Only 13 out of 23 patients with addisonian anæmia had even small amounts of proteolytic enzyme acting at pH 2·0, but 20 out of 23 had measurable activity between pH 2·6 and pH 5·0.[5] From further study it seems that in gastric juice from man there are two main pepsins—that is, proteolytic enzymes acting below pH 5·0. Moreover, one of these predominates in the pyloric mucosa and the other in the mucosa of the fundus and body of the stomach.[10] The results of an examination of gastric secretion from patients with peptic ulcer [11] or addisonian anæmia [5] suggest to TAYLOR that in some circumstances the gastric mucosa may secrete abnormal pepsins.

The main change of view resulting from TAYLOR'S work is that proteolysis in the gastric contents is not dependent upon such high acidities as was previously thought. As a consequence it now seems possible that gastric lipase [12] and salivary amylase, which have maximal activity at very low acidities, and gastric proteases, could all act more or less simultaneously in the same medium.

Having considered what types of digestion could take place in the gastric contents it remains to discover to what extent food is digested before it is passed into the duodenum. In view of the usual presence of acid and pepsin in the gastric contents it would be expected that the gastric digestion of protein would make a significant contribution to absorption. In the studies of MALTBY,[13] who gave 100 g. of fried minced lean meat and 300 ml. of water as a test-meal, the aspirated gastric contents contained as little as 25% unaltered protein when the pH was between 1 and 2. Even when the gastric contents were as weakly acid as pH 5 about a third of the protein was found to be partly digested, which gives in-vivo support to the views of TAYLOR: on the other hand, in MALTBY'S investigations patients with addisonian anæmia accomplished very little or no digestion of meat. Although an exact comparison is impossible because of differences in chemical methods, it is interesting to compare the degree of digestion of meat under MALTBY'S conditions, which were particularly favourable, with that reported by BEAZELL [14] with normal meals which were recovered from the stomachs of 2 subjects who could vomit at will. About 40% of the starch was digested in thirty minutes but practically none of the protein was completely digested. BEAZELL also points out that much of the meal had left the stomach before digestion of protein had taken place.

The idea that the stomach retains its contents until digestion is completed and only then transfers them to the duodenum should have begun to die with the appearance of BEAUMONT'S monograph in 1833 and was convincingly refuted by MCLURE et al.,[15] who showed that normal food began to leave the stomach within three to ten minutes of beginning a meal. Nevertheless the concept of retention till digestion is completed is given in a current textbook. Not only is gastric digestion of protein usually slow but much of the protein of a meal may have left the stomach before significant digestion could be achieved.

Since the stomach has an incomplete action in digesting protein and begins to empty its contents into the duodenum very shortly after a meal is taken, it is reasonable to ask whether or not it makes any important contribution to digestive function. Gastric emptying is not at all haphazard: the rate of gastric emptying becomes slower as the concentration of nutritive material in the original meal is increased. This regulation appears to be achieved via duodenal receptors which detect the products of hydrolysis of starch or protein, possibly by virtue of their osmotic pressure.[16] There is the well-known slowing of gastric emptying in response to fat, which increases with the amount of fat in the meal.[17] Gastric emptying is also adjusted in response to the initial volume of meals—for instance, the pattern of emptying with large meals is such as to give a sudden charge to the small intestine when the meal is eaten,

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2. Ihre, B. J. E. *Acta med. scand.* 1938, suppl. 95.
3. Wilkinson, J. F. *Lancet*, 1949, i, 249.
4. Janowitz, H. D. Quoted in *Physiol. Rev.* 1959, **39**, 492.
5. Taylor, W. H. *J. clin. Path.* 1959, **12**, 210.
6. Freudenberg, E. *Enzymologia*, 1940, **8**, 385.
7. Schwann, T. *Arch. Anat. Physiol., Lpz.* 1836, p. 90.
8. Taylor, W. H. *Biochem. J.* 1959, **71**, 73.
9. Anson, M. L., Mirsky, A. E. *J. gen. Physiol.* 1932, **16**, 59.
10. Taylor, W. H. *Biochem. J.* 1959, **71**, 384.
11. Taylor W. H. *J. clin. Path.* 1959, **12**, 338.
12. Schonheyder, F., Volquartz, K. *Acta physiol. scand.* 1946, **11**, 349.
13. Maltby, E. J. *J. clin. Invest.* 1934, **13**, 193.
14. Beazell, J. M. *Amer. J. Physiol.* 1941, **132**, 42.
15. McLure, C. W., Reynolds. L., Schwartz, C. O. *Arch. intern. Med.* 1920, **26**, 410.
16. Hunt, J. N. Macdonald, I., Spurrell, W. R. *J. Physiol.* 1951, **115**, 185.
17. Annegers, J. H., Ivy, A. C. *Amer. J. Physiol.* 1947, **150**, 461.

followed by a slowly diminishing trickle of material which presumably matches the absorption.[18]

Nutritional disorders after total and partial gastrectomy are common,[19] and their study has made apparent the part which the stomach plays in digestive processes. In particular the effect on the total digestive processes of bypassing the duodenum has become clearer. The masterly study of LUNDH,[20] using new techniques with radio-tagged fat and protein and an inert marker, has shown that after Bilroth-II operations there is a notable failure of mixing of trypsin with the intestinal content, the absorption of protein in his patients being more abnormal than the absorption of fat. After partial gastrectomy LUNDH found that the absorption of protein was correlated with the concentration of trypsin in the intestinal contents, whereas in normal persons these values were independent. This finding was taken to indicate defective peptic digestion, thus putting the tryptic phase under strain. The current interest in the digestion and absorption of protein in such patients is a fitting response to the emphasis laid by BRAIN and STAMMERS [19] on the need for studying nutrients other than fat in patients with metabolic difficulties after gastrectomy.

There is a big functional reserve to the various components of the digestive tract, and, other things being normal, gastric digestion *is* dispensable; but the gastric reservoir function is important for the proper time relationships between presenting material to the intestine and evoking the secretions of the pancreas. Moreover, various subjective disturbances are common after gastrectomy, apparently as a result of too rapid filling of the intestine.[21]

18. Hunt, J. N., Macdonald, I. *J. Physiol.* 1954, **126**, 459.
19. Brain, R. H. F., Stammers, F. A. R. *Lancet*, i, 1951, 1137.
20. Lundh, G. *Acta chir. scand.* 1958, suppl. 231.
21. LeQuesne, L. P., Hobsley, M., Hand, B. H. *Brit. med. J.* 1960, i, 141.

Annotations

MIRAGE OF HEALTH

WE are all specialists now, and it is notorious that a surgeon on biochemistry and a biochemist on surgery are equally likely to talk rubbish. Such trespasses in other demesnes are not however always disastrous and can be most illuminating. Dr. René Dubos is one of the most distinguished of living bacteriologists and his essay, *Mirage of Health*,[1] ranges almost every field of medicine and far beyond. The basis of his argument is that the formula:

Host + specific parasite = specific disease

is seldom if ever true. Somewhere on the left side of the equation are other factors, some of which we know so well that we tend to forget them and others which in our ignorance we have barely recognised. Because perhaps Pasteur's *Memoire sur la fermentation* . . . was contemporary with talk about " the struggle for existence ", our profession has tended to treat all bacteria as enemies: the only good microbe is a dead microbe. If the slogan " Kill that germ " was applied conscientiously we would not only lack cheese and beer but most of us would die either of a deficiency of vitamins or by infection by organisms with which we now live in happy symbiosis. There are, in fact, few bacteria which cannot survive in the human body without harm to either party: bacterial disease is an upset of this mutual tolerance by the missing factors in the equation. Even in such infections as gonorrhœa where these factors seem of small account a perfect prophylactic and treatment has not extinguished the disease. For this we need an understanding of social habits which we have not got.

History suggests that the most venomous epidemics are those imported into a society where the " causative " organism has been hitherto unknown. Measles reduced the population of Fiji by one-quarter in one year. (It is a curious fact that the import of diseases from the temperate zone into the virgin populations of the tropics has done far more damage than the reverse traffic. Have our institutes of tropical medicine been looking in the wrong direction?) The lethal consequences of these introductions have been shortlived, and quite quickly adaptations in the host (and perhaps the parasite) make the disease no more deadly than it was in its original home. At this moment the phenomenon is exemplified by myxomatosis in the rabbit. The infectious diseases which plague us day in day out seldom come in epidemics but are the result of minor changes in the internal and external environments—fatigue, diabetes, perhaps worry—which supply the missing factors in the equation. The deaths in concentration camps were due to our common diseases occurring more frequently and with greater virulence. Our ecological balance is indeed precarious and (which is more important) always changing. So long as the changes come slowly we can usually adapt ourselves to them individually and as a race. Disaster is the consequence of great changes made too abruptly: the sedentary man running for a train or the prize cattle breathing London smog. One of the great difficulties of planning for health (or for war or even holidays) is that experience is of limited value. We can do no more than guess the dangers ahead and our surmises are not always correct.

Every civilisation has cherished a dream of perfect health and happiness, usually in the dim past or far far away. Today we tend to look forward. " Health is purchasable ", and we see all round us new projects, new committees, and new buildings. We owe much to the laboratory but perhaps not so much as we think. The changes in environmental hygiene which freed us from typhoid and typhus—clean food, clean water, clean air—were devised and implemented by men who had never heard of bacteria. Antibiotics have reduced mortality but may have added to morbidity. By design the experimentalist limits the conditions of his inquiry to obtain a clear and certain answer. The manifold factors which decide the larger issues of health and disease in ourselves, our homes, our community, and our nation are too complex as yet for comparable analysis. Are our criteria of health beyond criticism? The legend of the " bonny baby " was exploded years ago and survives only at rural baby shows. Those who talk comfortably of " the conquest of disease " should remember that at 45 our expectation of life is not much better than that of our grandsires: every year we find it necessary to spend more and more on health (and in the U.S.A., Dr. Dubos says, this amounts to 10% of personal income): and at least one in ten of us will spend some days, weeks, or months in a mental hospital.

1. Mirage of Health: Utopias, Progress and Biological Change. By RENÉ DUBOS. London: Allen & Unwin. 1960. Pp. 221. 21s.

On and around these matters Dr. Dubos has written an exceptional book—plain, lucid, elegant, and lively. It draws its facts and illustrations not only from the corpus of medicine but from authors from Lao-tzu to Proust. It is logical and persuasive rather than dogmatic. It is in fact a confession of faith and humility by a great scientist. We commonly hear the complaint that the young doctor of today knows more and more about less and less. Reading Dr. Dubos' book will make him a more useful member of our profession than an exact memory of the seventeen causes of enlargement of the spleen—and in this respect we are all young doctors.

PERTHES' DISEASE

Perthes' disease is now one of the commonest disorders of the hip in childhood. It affects children mainly between the ages of 3 and 8, and the symptoms are often trifling. There is occasional pain in the leg, a limp which may be difficult to detect, and some limitation of abduction and internal rotation. The radiographs may remain normal for some months after the onset of symptoms; but, when changes do appear, the head and neck of the femur undergo a slow process of disorganisation and reformation over a period of two, three, or more years.

O'Garra [1] distinguishes two types of radiological changes in the femoral head, depending on whether the whole of the head is affected, or only the anterior half or two-thirds, and suggests that the prognosis is more favourable with incomplete involvement. Of much greater importance is the age of onset and the sex of the patient. Using the final shape of the head as an index of resolution—and there is little else one can rely on in the child—there can be no doubt that girls do less well than boys. On similar criteria the younger the age of onset the better the prognosis. Until these two factors have been considered in O'Garra's figures, it is hard to tell whether partial head necrosis carries a better prognosis than complete necrosis, although the assumption seems reasonable.

No general agreement has been reached upon the pathogenesis of Perthes' disease. The radiological changes suggest an initial necrosis of bone, followed by reconstruction. Histological studies [2] of biopsy material from 23 hips confirm that necrosis affects the marrow, cartilage, and bone of the femoral head. Ponsetti [3] suggests that these changes are secondary to disruption of the epiphyseal cartilage plate, and are due to a disturbance of the blood-supply as the retinacular vessels cross the disrupted epiphyseal plate. That the lesion is one of avascular necrosis was first proposed by Legg [4] and is still the most commonly accepted view. Cavanaugh et al.[5] suggested that osteochondritis of the femoral head is associated with a high incidence of colloid goitre in the families of affected patients, but Beiler and Love [6] were unable to find evidence of hypothyroidism in a group of patients with Perthes' disease. Similar radiological changes, however, may be present in the cretin and the mongol, and in the reticuloses and certain other general affections of the skeleton. In these conditions progressive destruction and replacement of the femoral head is absent.

Most patients with Perthes' disease are treated by some method which attempts to relieve weightbearing in the leg. In some centres rest in bed with traction is considered essential until the head begins to reform. Other surgeons suggest that a weight-relieving calliper is adequate, and Evans and Lloyd Roberts [7] believe that recumbency has no advantage over an ambulant method of treatment. Many would agree with Legg [8] that relief from weightbearing in no way affects the end-result. Before committing these children to a period of institutional treatment which may well last a year or more, two things must be established: firstly, that the prognosis of the untreated disease is sufficiently grave to justify this line of treatment; and secondly that prolonged treatment in recumbency improves the prognosis. Of the long-term effects of Perthes' disease little is known. Ratliff [9] has shown that, although radiological changes may persist in the hip into early adult life, function is rarely affected at this age. If, as seems likely, osteoarthritis is an uncommon sequel there can be little justification for long-term orthopædic treatment in childhood.

PROGNOSIS IN GENITOURINARY TUBERCULOSIS

THE place of combined chemotherapy in the treatment of urogenital tuberculosis is now so secure that it is hard to recollect the former ravages of the disease and to appreciate what has been accomplished. Barely twelve years have passed since the introduction of streptomycin (followed shortly afterwards by *p*-aminosalicylic acid and later by isoniazid), and a sufficient interval has only just elapsed to allow a full appraisal of its effect on what is often a chronic disease. In this respect the report of Gale and Kerr [10] from the Toronto Hospital for Tuberculosis is of outstanding importance, not only for its large number of treated cases but for the almost similar number of earlier cases which serve as a control. Historically Toronto has a special interest in the disease since it was here in 1929 that Harris [11] did his classical work on the association between renal and orthopædic tuberculosis. Some of his original patients are now included in a group of 82 cases followed for upwards of thirty-five years, and they represent an era when neither nephrectomy nor chemotherapy was in use. These cases give a remarkable picture of what used to be the natural history of tuberculosis, with a mortality-rate of 40% within five years and an eventual survival of 32% (described as " good chronics ") in which something approaching symbiosis was fortuitously achieved between host and invader.

It might be assumed that with the subsequent vogue for nephrectomy in unilateral disease these morbidity statistics would improve; but in a further series of 347 consecutive cases treated where indicated by nephrectomy there was little apparent change. 43% died within five years, although 48% were still surviving over a period extending up to fifteen years. By contrast, however, the addition of chemotherapy—and in particular triple-drug therapy—is shown to be outstandingly effective. In a third series of 389 cases treated by a combination of nephrectomy (where indicated) and chemotherapy, followed for a period of up to ten years, the mortality-rate fell to 4%. Of the last 214 consecutive patients in this series receiving six or more months of chemotherapy none died from renal

1. O'Garra, J. A. *J. Bone Jt Surg.* 1959, **41B**, 465.
2. Haythorn, S. R. *ibid.* 1949, **31**, 599.
3. Ponsetti, I. V. *ibid.* 1956, **38A**, 71.
4. Legg, A. T. *Boston med. surg. J.* 1910, **162**, 202.
5. Cavanaugh, L. A., Shelton, E. K., Sutherland, R. *J. Bone Jt Surg.* 1936, **18**, 957.
6. Beiler, D. D., Love, W. H. *ibid.* 1956, **38A**, 320.
7. Evans, D. L., Lloyd Roberts, G. C. *ibid.* 1957, **39B**, 782.
8. Legg, A. T. *ibid.* 1927, **9**, 26.
9. Ratliff, A. H. C. *ibid.* 1956, **38B**, 498.
10. Gale, G. L., Kerr, W. K. *Canad. med. Ass. J.* 1959, **81**, 977.
11. Harris, R. I. *Brit. J. Surg.* 1929, **16**, 464.

tuberculosis. Whereas this phenomenal improvement is undoubtedly largely due to sustained triple-drug therapy, Gale and Kerr also acknowledge the ancillary benefit of certain conservative and reconstructive surgical procedures thereby made possible. They rightly claim, however, that progress in the management of genitourinary tuberculosis during the past ten years ranks paramount among all the remarkable advances in urology within this period.

TEMPERATURE REGULATION DURING FEVER

THOUGH fever is a very common accompaniment of disease or tissue damage, elevation of body temperature does not in itself clearly benefit the patient, except perhaps in a few special situations. For this reason fever is sometimes regarded as a manifestation of failure of the normal controlling system; but this is far from the truth. For many years there has been evidence suggesting that the body temperature is controlled at a higher level in disease.

The concept of fever as a change in the setting of a central thermostatic mechanism was first formulated by Von Liebermeister,[1] and subsequent work by Stern [2] substantiated this hypothesis. Stern observed the development of sweating or of shivering in patients with and without fevers, when they were warmed or cooled by gradually changing the temperature of a bath in which they sat. He found that the change in rectal temperature when patients began to sweat or to shiver was the same in the pyrexial and apyrexial groups. Subsequent experimental work in man has in general confirmed these findings. Park and Palmes [3] found that the injection of bacterial pyrogens into normal subjects produced the same elevation of temperature in warm or cold environments. All these findings suggest active regulation of body temperature during fever, though the evidence is not entirely conclusive.

Further convincing evidence of active temperature control has been described by MacPherson.[4] In a long series of experiments he obtained very complete records of the responses of three normal subjects to standard exercise during environmental heat stress. During these experiments one subject developed a febrile illness characterised by cough and malaise; his temperature was raised by 0·5–1·5°F for six days. During this time the subject was able and willing to continue with the experiment, thereby providing very interesting information.

Before the onset of fever this subject responded to exercise with an increase of rectal temperature which was almost identical with that of his companions. During the fever this pattern was exactly reproduced, at a higher level. The absolute temperature increment due to exercise remained the same. During exercise at moderate environmental temperatures the normal subjects showed a fall of skin temperature, with recovery during the subsequent rest period. This pattern was also reproduced by the febrile subject, at a higher absolute temperature level. During exercise this subject's sweat-rate did not differ significantly from that of his companions.

These experiments confirm and extend the previous findings, suggesting that the febrile patient responds to various thermal stimuli in much the same way as the normal subject, but at a higher level of temperature. It is difficult to avoid the conclusion that his temperature is regulated in the same way. If the regulating mechanism is normally active, the temperature rise in fever must be actively produced. Why this happens is unknown.

1. Von Liebermeister, C. Handbuch der Pathologie und Therapie des Fiebers. Leipzig, 1875.
2. Stern, R. *Z. klin. Med.* 1892, **20**, 63.
3. Park, C. R., Palmes, E. D. Medical Department Field Research Laboratory, project no. 6-64-12-06. Fort Knox, Ky, 1948.
4. MacPherson, R. K. *Clin. Sci.* 1959, **18**, 281.

B.P.C. 1959

THE new edition[1] of the *British Pharmaceutical Codex* is dated 1959—a vintage year for official publications on prescribing costs—and against this background the *B.P.C.* assumes great importance. The conscientious and selective use of the *Codex* by medical students and doctors would encourage the critical attitude and keener appreciation of the place of pharmacy in relation to therapeutics that can lead to prescribing which is both sound and economical.

It is strange that the *British Pharmacopœia* (published under the ægis of the General Medical Council) continues to be a book of reference used almost exclusively by pharmacists, while the *Codex* (published by the Pharmaceutical Society of Great Britain) has become one of the most important books available to doctors. The subject matter of the two is, of course, much the same, but there are striking differences in presentation. Thus, the *Codex* includes paragraphs on the actions and uses of drugs: these are not intended to convert it into a textbook of pharmacology, but they are invaluable in presenting concise information about the effects of drugs and the relative merits of their various preparations. Thus, the *Codex* is a book of capital importance as an ancillary to standard works on therapeutics.

Although drugs, or particular preparations of drugs, which have been deleted from the *Pharmacopœia* are likely to disappear also from the *Codex*, it is the traditional policy of the *Codex* Revision Committee to retain many of these preparations, if they are widely used, and look at them occasionally during a further period of five years. There is clearly a place for this conservative attitude, for although the factual data of the *Pharmacopœia* and *Codex* inevitably have much in common, the books are in many ways complementary. Allowance must also be made for doctors who are not prepared to modify their prescribing habits simply because, for various reasons, certain pharmaceutical preparations are no longer " official ".

The additions to the new *Codex* include 70 new general monographs, and 20 of these refer to drugs already included in the *B.P.* 1958. Among the monographs which deal with the more specialised materials (biological products, surgical ligatures, and sutures), poliomyelitis vaccine and rabies antiserum deserve mention. The Formulary (part VI of the *Codex*)—perhaps the most valuable section for the prescriber—contains some 79 new items, but 44 of them represent " salvage " from those deleted from the *B.P.* There are long lists of deletions under monographs and under formulary. Some 26 preparations suffer total eclipse, in that they no longer appear in either the *B.P.* 1958 or the *Codex* 1959. But few doctors will feel their withers wrung by the demise of infusion of quassia, solution of mercuric chloride, and the dilute solution of ammonium acetate. The rise and fall of creams of penicillin (also among the 26 condemned to the twilight of obscurity) may, however, cause some to reflect on the transient glories of therapeutic fame.

1. British Pharmaceutical Codex 1959. 7th ed. Council of the Pharmaceutical Society of Great Britain. London: Pharmaceutical Press. 1959. Pp. 1301. 70s. The *Codex* comes into force in the United Kingdom on July 1, 1960.

Public Health

EFFICACY OF AN ANTI-SMOKING CAMPAIGN

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THE scientific status of health education is not impressively high. Though more and more importance is attached to it as a function of the public-health services, there has been a notable shortage in this country both of theoretical analyses of the assumptions upon which health education is based and of evaluative studies of specific campaigns. Intention and effect have too often been confused, and the success of a programme has been measured by the enthusiasm with which it was planned and executed.

If educational measures are to be the principal means of trying to reduce current levels of tobacco consumption, assessment of their value is as important as assessment of the value of more conventional prophylactic procedures. Some local health authorities have already responded to the recommendation of the Ministry of Health and the Department of Health for Scotland that they should bring home to the public the health hazards associated with cigarette smoking, and many more may be planning to do so. The experience of the Edinburgh Health Department, which carried out a fairly extensive anti-smoking campaign and asked the University Department of Public Health and Social Medicine to evaluate its efforts, may therefore be of some interest.

The Campaign

The budget for the campaign totalled £4350—corresponding to about 2¼*d.* per head of population—although certain additional money was available in the ordinary course of health education expenditure. The campaign was developed on the following lines:

Press.—Paid display-advertising material in which the Medical Officer of Health warned the public of the danger of cigarette smoking was accepted by all newspapers with a wide local circulation. Each of the three Edinburgh newspapers also gave the campaign powerful editorial support and provided much space in its news columns, gossip column, sports page, and photographic sections. Support from the national Press was considerable though less extensive.

Posters.—About 120 16-sheet posters were displayed on hoardings throughout the city, and about 3000 double-crown and crown posters were displayed in factories, offices, clubs, clinics, consulting-rooms, libraries, public baths, and shops. A poster was also shown in all the buses in Edinburgh.

Leaflets and letters.—30,000 copies of the British Medical Association's booklet *Smoking—the Facts* were distributed at meetings and to schoolchildren. A special Edinburgh campaign leaflet was designed by one of Britain's foremost display artists, and 150,000 copies were distributed through a variety of channels. A clear and forceful letter from the Medical Officer of Health was sent to every household in Edinburgh.

Meetings.—24 meetings were held at which over 2600 teachers heard the case against smoking presented by a doctor using visual aids in the form of a specially prepared flannelgraph and the B.B.C.'s film *Facts and Figures—Smoking and Lung Cancer*. Every class of secondary-school children was visited by a medical member of the Health Department. Meetings were arranged with almost all the parent-teacher groups in Edinburgh, at which the film *1 in 20,000* was shown. About 70 public meetings were held in different parts of the city in cooperation with various associations, clubs, &c.

Other media included a rally of voluntary workers, a concert for young people, a Sunday cinema meeting, and radio and television publicity.

The Evaluation

Two parallel samples of the adult population of the city were drawn, one sample to be interviewed before the opening of the campaign, in November, 1958, and the other to be interviewed six months later. The object was to discover any shift in the distribution of smoking habits and/or of associated beliefs.

The methods of sampling and interviewing have been described by Cartwright, Martin, and Thomson (1959a). 590 interviews were completed before the campaign and 596 after it: these correspond to response-rates of 85% after removal from the initial samples of those who had died or left their original address between the compilation of the electoral register and the survey period.

Smoking Habits

There was no indication that the campaign persuaded people to give up smoking. Similar proportions of people in the two surveys said that they smoked regularly—that is, at least one cigarette a day—and there was no significant change in the proportion who claimed to have given up smoking.*

The forms of tobacco consumption also remained unaltered; the ratio of pipe to cigarette smokers was similar on the two inquiries and there was no evidence that filter-tipped cigarettes or cigars had increased in popularity.

These negative findings are confirmed by the replies given to a direct question included in the second inquiry. Not one of our informants claimed to have given up smoking, even temporarily, as a result of the campaign, although, curiously enough, as many as 12% of all the people interviewed claimed to know someone who had stopped smoking because of the campaign. On the other hand, 9% of the smokers thought that their smoking habits had been influenced by the campaign; the majority of these claimed that they had been persuaded to smoke fewer cigarettes. Similarly, when the members of our samples were asked whether they were smoking more, less, or the same amount as six months previously, a comparison of pre-campaign and post-campaign replies suggested that a higher proportion of those interviewed in May, 1959, were under the impression that they had reduced their tobacco consumption. But when we compared the actual levels of tobacco consumption reported before and after the campaign we found no significant difference. It is very possible that the campaign succeeded in persuading a number of people to try to smoke less, and that in retrospect they may have felt their attempt to have been more successful than it was.

Beliefs about the Health Hazards of Smoking

Our November inquiry had shown that all but 2% of the adult population had already heard of the postulated connection between lung cancer and smoking, although many of them regarded the theory with varying degrees of scepticism. Hence there was virtually no scope for raising the level of public awareness of the hypothesis; and indeed after the campaign the proportion who maintained that they had not heard of it was still about the same.

* Copies of statistical tables which give the findings in detail may be had from the authors.

On the other hand, there was a considerable opportunity to convince people that the hypothesis is correct. Yet after the campaign the proportion prepared to accept it was found not to have risen significantly ($P > 0.05$). In spite then of the repeated warnings of the Medical Officer of Health almost as many people were still unwilling to believe that lung cancer is more likely in smokers than in non-smokers.

In the first (pre-campaign) inquiry people were rather more ready to attribute such ill effects as coughs, breathlessness, bronchitis, and catarrh to smoking than they were to admit that it could cause cancer. As these conditions were not mentioned in the campaign publicity, it was perhaps surprising to find a significant rise in the proportion who thought smokers more liable to breathlessness, bronchitis, coughs, catarrh, or heart-disease than non-smokers, although there was no change in the proportion who thought smokers more liable to indigestion, rheumatism, stomach ulcer, or tuberculosis.

Similarly, although the campaign did not increase the proportion of smokers who supposed that smoking had affected their own health, it did produce a notable increase —from one in five to one in three—in the number who believed that their health might be adversely affected in the future. This change was brought about by more smokers specifying breathlessness and cough as possible future effects; the proportion mentioning cancer as a personal risk did not rise significantly.

This greater readiness to accept smoking as a possible cause of conditions which are more common and for the most part more trivial than lung cancer was wholly unexpected. Two causal processes appear to be involved.

The first of these could be a form of emotional blockage. The widespread fear of cancer—long nurtured by a conspiracy of silence—generates a resistance that factual assertions do not easily overcome. This resistance is strengthened by the feeling of guilt which may be aroused by incrimination of a habit which the individual knows that he ought to be able to control.

The second process is one of deflection and dilution: the charge against smoking is translated into terms which are more familiar and more acceptable. Before the campaign there had been no great reluctance to concede that smoking might be harmful to health, and afterwards there was an even more widespread readiness to recognise its hazards. But they are hazards more commonplace than lung cancer and on the whole far less frightening. This latter tendency has affinities with the process of explaining the ætiology of major diseases in terms of simple everyday hazards, which we have called " reduction to the familiar " (Cartwright and Martin 1958, Cartwright, Martin and Thomson 1958).

The anti-smoking campaign, then, apparently heightened public awareness of some of the possible effects of smoking upon health, but did not increase acceptance of the idea that cigarette smoking may cause lung cancer.

General Attitudes to Smoking

One of the more hopeful findings of the pre-campaign inquiry was that just over two-fifths of current smokers said that they would like to give up smoking if they could do so easily. This proportion had not increased after the campaign, nor had there been any change in the pattern of reasons put forward for wishing to give up smoking. Before and after, expense was most commonly cited; fear of cancer was mentioned by only 2–3% of smokers, and other health reasons were given by about one smoker in seven.

Some change was evident, however, in attitudes towards smoking in young people. Whereas before the campaign slightly under two-thirds of our informants felt it was " wrong " for young people to start smoking, by May this proportion had risen to just over seven-tenths. Similarly, after the campaign, parents with children above the age of 15 were more inclined either to regret that their children smoked or to rejoice that they did not.

Beliefs as to the advantages of smoking also seemed to have been modified slightly. There was a little more scepticism about the view that smoking helps people to relax, 11% rejecting it compared with only 6% six months earlier. Nevertheless it was still accepted by four-fifths of the post-campaign sample, while a similar proportion thought that a cigarette helps to relieve nervousness or embarrassment. This latter fraction had not changed during the campaign.

In general, then, there does appear to have been a very modest change in public attitudes. There is certainly nothing to suggest that smoking was becoming socially unacceptable; but there was probably a slightly wider acceptance of the idea that one ought not to encourage young people to start it.

Perception and Recall of the Campaign

To discover the extent of public awareness of the campaign, our post-campaign sample were first asked whether they had heard, seen, or read anything in the past few months about smoking and lung cancer. Nearly three-quarters said that they had.

Newspaper articles were recalled more often than any other form of publicity. They were mentioned spontaneously by just over half our informants, compared with slightly more than a quarter who mentioned posters. Other forms of publicity, such as leaflets and radio and television programmes, were recalled spontaneously by less than a tenth. However, the proportions who claimed to have noticed the various publicity media rose appreciably when specific questions were asked. Newspaper publicity was recollected by a further 20% (so that altogether nearly three-quarters of our sample claimed to have noticed this) and two-thirds had seen posters. The posters displayed on buses seem to have had substantially more impact than those on the hoardings. Meetings and film shows had been attended by only 2% and 3% respectively. Only 15% reported having seen a leaflet on smoking and lung cancer, though the Public Health Department had circulated 150,000 copies—one for every three persons in the city. Similarly, rather less than a third said that their household had received a letter from the Medical Officer of Health, although such a letter was supposed to have been sent to every householder in Edinburgh.

After asking questions about the specific aspects of the campaign, our interviewers said, " These things were, in fact, all part of a campaign about the connection between lung cancer and cigarette smoking. Did you know there had been a campaign ?" Replies show that a fifth of the adults in our sample had been unaware of it.

Men were rather more likely than women to know about the campaign. More of them had read about it in the newspapers and seen the posters on the buses and on the hoardings. There was no difference between the sexes in the proportion who had seen any films or leaflets, attended meetings, or received a letter from the Medical Officer of Health.

The campaign also had rather more impact on younger than on older people. The proportions who were aware of the campaign or who had seen the posters or who had seen a leaflet were significantly lower among people aged 55 or more. In contrast, the proportion who had read anything in the newspapers did not fall off to any appreciable extent with increasing age.

The group of semi-skilled and unskilled workers and their wives was rather less aware of the campaign than those in skilled manual work, while the most widespread awareness was

found among professional and blackcoated workers and their wives. A similar trend was also shown for certain specific aspects of the campaign—newspaper publicity and letters from the Medical Officer of Health; but posters in buses were less often noticed by the middle-class members of our sample.

These factors—sex, social class, and to a lesser extent age—are all associated with differences in smoking habits (Cartwright, Martin, and Thomson 1959a); the category of smokers, compared with that of non-smokers, contains higher ratios of men to women, of younger to older women, of unskilled to skilled manual workers, and of manual to blackcoated workers. It is not surprising, therefore, to find that the impact of the campaign varies as between groups classified according to smoking habits. The small numbers involved make cross-analyses difficult to interpret, but they seem to suggest that the variations may be explained largely in terms of the different sex, age, and social class characteristics of smokers and non-smokers respectively.

Compared with people who were non-smokers or occasional smokers or people who had given up smoking, smokers were more inclined to say they had noticed something about the connection between lung cancer and smoking in the last few months. On the other hand, they were less likely to have attended any meetings or to have noticed the letter which was sent to householders by the Medical Officer of Health. There was no significant difference between smokers, non-smokers, and others in the proportion who had read anything in the newspapers or noticed the posters on the hoardings, but among the non-smokers a smaller proportion had seen the posters in buses or were aware that there had been a campaign.

Discussion

Although the anti-smoking campaign reached a large majority of the city's adult population through one medium or another, its coverage by no means equalled that achieved in the mass-radiography campaign a year before. The latter, though concentrated into a much shorter period, had an impact upon almost the entire community (Cartwright, Martin, and Thomson 1959b). Newspaper and poster publicity in the mass-radiography campaign was seen and recalled by 95% and 91% of the population respectively, compared with 73% and 64% in the anti-smoking campaign.

If it was ever expected to have an immediate and appreciable effect upon smoking habits, then the anti-smoking campaign must be deemed a failure, since our surveys showed no statistically significant shift in the distribution of these habits after the campaign. Failure in this sense might have been predicted from the outset; for our pre-campaign inquiry had shown that, although 98 adults in every 100 had heard of the possible association between lung cancer and smoking, the number who had therefore given up smoking was very very small.

Nor can the campaign be judged successful in having persuaded people that smoking does in fact increase the risk of lung cancer. Unexpectedly, it increased the proportion of people who thought smoking harmful to health in other ways; but there was no parallel increase even in the proportion of smokers who would like to give up smoking if they could do so easily. One cannot, of course, assume that a sustained campaign might not have a cumulative effect; the hardening of attitudes towards smoking among young people provides a hopeful indication, albeit on a modest scale. Nor may it be taken for granted that a campaign whose focus was directly upon either the minor health hazards or the expense of smoking might not have more rapid and significant effects.

It is arguable that educational campaigns of this nature are based upon unrealistic assumptions about perception and motivation. But, although their chances of bringing about direct and immediate changes are extremely slender, they may in the long run help to change the climate of opinion in such a way that young people become less likely to start smoking. Against this, the difficulty which habitual smokers experience in giving up the practice makes it improbable that large-scale changes can be accomplished until ways can be found of assisting the many people who would like to stop smoking but cannot do so by their own unaided efforts.

Summary

A health education campaign in which the Edinburgh Public Health Department tried to bring home to the public the risks of lung cancer associated with cigarette smoking was evaluated by the Edinburgh University Department of Public Health and Social Medicine. The evaluation was based upon interviews with random samples of the adult population of the city—590 before the campaign and 596 six months later.

The campaign did not increase the proportion of non-smokers in the population, and the ratio of heavy to light smokers remained unchanged. Nor was there any significant increase in the proportion who believed that smoking may cause cancer of the lung. There was, however, a rise in the proportion who thought that smoking could be harmful to health in other ways—e.g., in causing cough—though these had not been mentioned in the campaign.

No change was evident in the nature and extent of smokers' ambitions to alter their own habits, but a greater proportion of those interviewed thought it undesirable that young people should start smoking.

About three in four of our informants reported having been aware of the campaign; newspaper articles and posters were the only publicity media frequently mentioned. Awareness of the campaign as a whole and of specific forms of publicity were found to vary with age, sex, and occupational class.

Campaigns of this type are unlikely to produce changes in behaviour except possibly in an indirect and long-term fashion.

This inquiry was supported by grants from the Chest and Heart Association (formerly the National Association for the Prevention of Tuberculosis) and from the British Empire Cancer Campaign. We should also like to acknowledge the help and encouragement of Prof. J. H. F. Brotherston, Prof. John Crofton, and Dr. H. E. Seiler, and the valuable assistance of Miss Alice Stephen.

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Extension of Poliomyelitis Vaccination

The Minister of Health announced on Monday that the age limit for free poliomyelitis vaccination is being raised to cover all persons who at the time of their application for vaccination are under 40. The following small groups will also be offered vaccination:

(*a*) Persons going to visit or reside in a country outside Europe, other than Canada or the United States of America.

(*b*) Practising dental surgeons, dental students, dental hygienists, student hygienists, dental surgeons' chairside assistants, and their families.

(*c*) Practising nurses not working in hospitals (those working in hospital are already eligible) and their families.

(*d*) Public-health staff who might come into contact with poliomyelitis cases, and their families.

In a letter to local health authorities the Minister says these extensions are based on the advice of the Joint Committee on Poliomyelitis Vaccine. At the same time the committee recommend that efforts should continue to be directed to the vaccination of as many as possible in the existing priority groups. "Thus, although the acceptance rate among children born since 1943 is generally high, special efforts are still required in those areas where the rate is below the national average; and the need for raising the rate among expectant mothers continues in most areas. Authorities have, with the co-operation of general practitioners, and by hard work and imaginative publicity measures, to a large degree surmounted the difficulties encountered in obtaining a satisfactory response from the group born between 1933 and 1942." Executive councils are also sending a letter to all family doctors about the extension of the programme.

By the end of last year registrations for vaccination passed the 13 million mark. Nearly all of those registered had had at least two doses of vaccine and over 7·3 million had received three. In the 16–26 age-group, a total of about 2·7 million, or 46% of those eligible, had registered, and almost all had had at least two injections. For children (1943–59 age-group) the acceptance rate rose to 75·4%, and 9·5 million had received two or more doses.

The provisional number of cases of paralytic poliomyelitis last year fell below 1000 for the first time for 13 years: the total was 914. The provisional number of both paralytic and non-paralytic cases was 1345, which was also the lowest since 1947. It compared with 2370 in 1958. The previous lowest total was 2177 in 1948. The highest number of cases notified in any one week during 1959 was 58 for the week ended Aug. 22. The lowest figure was two cases during the week ended Dec. 26. This is the lowest number for any week since the last week in 1946 when only one case was notified.

1959

Provisional figures for England and Wales in 1959 were published on Jan. 23 by the Registrar General in his weekly return.

The number of *live births* was 750,170—i.e., 16·5 per 1000 population, which is the highest rate since 1949. *Infant mortality* was 22·0 per 1000 live births (22·6 in 1958, 23·1 in 1957, 23·7 in 1956, and 32·4 in 1949). The death-rate was 11·6 per 1000 population (11·7 in 1958 and 11·5 in 1957). The *excess of births over deaths* registered in 1959 was 222,596, the biggest since 1948, when it was 307,072. 15,009 *stillbirths* were registered in the year, giving a rate of 20·7 per 1000 live and still births (21·6 in 1958 and 22·5 in 1957).

Health Statistics for Scotland

The Department of Health for Scotland has published the first [1] of a new series of annual reports giving detailed statistics about health and health services in Scotland. It deals with 1958 and gives more detailed figures over a wider range than have so far appeared in Scotland in a single volume.

Until 1958, the annual reports of the Department of Health included statistical information about health services. It was decided that the ordinary departmental report for 1958 (already published) should include only limited statistical material, and that a separate more detailed volume of health statistics should be published. It includes population and other vital statistics and figures showing causes of death and illness in Scotland in 1958. Under some heads it covers a number of years before 1958. In the section on the hospital and specialist services, comprehensive figures are given showing the number of beds used for various types of illness in the regions, and the number of staff of different types employed in the hospitals. There are also sections on the maternity services, infant and child health, and general medical, dental, and ophthalmic services. Another section gives figures showing the cost of the health service under various heads.

1. Department of Health for Scotland. Scottish Health Statistics 1958. H.M. Stationery Office. Pp. 205. 12*s*. 6*d*.

Conference

RADIATION PROTECTION AND MARROW TRANSPLANTATION

AT a conference held at the Oak Ridge National Laboratory, Tennessee, on Jan. 8–9, progress in protection against radiation was reported by various groups in the United States.

D. G. DOHERTY (Oak Ridge) said that no recently synthesised compounds tested had been superior to aminoethyl isothiourea (A.E.T.), for which maximum protective effect in mice gave an LD_{50} of 1100–1200r. D. P. JACOBUS (Walter Reed) had obtained good results with mercapto propyl- and ethyl-amines, and with 5-hydroxytryptamine there was significant protection in mice and rats, but not in dogs, apart from slight delay in fall of white-blood counts. J. MAISIN (Armed Forces Institute) had used tritium-labelled A.E.T. to determine its distribution in the mouse after intraperitoneal injection. Autoradiographs appeared to show widespread uptake in liver, spleen, brain, kidney, lung, and pancreas, and also in spontaneous tumours such as ovarian adenocarcinoma, hepatoma, angiosarcoma, and reticulosarcoma; but it was not clear whether the material was intracellular or not.

Other workers in the Armed Forces Institute had shown marked protective synergism in mice, using A.E.T. and 5-hydroxytryptamine. At 2500r there was only a 25% mortality. V. DI STAFANO (Rochester) had found A.E.T. to have acetylcholine-like effects on the gut, which were blocked by atropine both in vivo and in vitro.

A.E.T. had been used clinically by J. V. SCHLOSSER (New Orleans) in more patients. There was no evidence of tumour protection, but so far there were too few controls to assess the degree of protection of the patient. M. KELLY (National Cancer Institute) presented good evidence from controlled experiments in dogs that A.E.T. did not protect tumours, but did protect the animals against radiation. J. A. COHEN (Netherlands) reported that the effect of A.E.T. on thymocyte protection in vitro correlated inversely with oxygen consumption and suggested that A.E.T. exerted its effect in vivo in this way.

BONE-MARROW TRANSPLANTATION

N. GENGOZIAN (Oak Ridge) reported his findings of differences in the antigen recognition mechanisms in mice, using red cells of different species. Sublethal irradiation lengthened the induction period following red-cell injection. The more closely related the donor species, the greater the lengthening. Young mice had longer induction periods than older mice and gave lower antibody titres. For effective heterologous marrow transplants in irradiated mice, larger quantities of cells were needed for the rabbit than the rat, the hamster being intermediate. W. DAMESHEK (Boston) had shown inhibition of antibody formation to soluble antigens by rabbits treated with 6-mercaptopurine in doses of 3–6 mg. per kg. Such failure of response persisted for about six months, as judged by response to further challenges with the same antigen, but there was no failure of immunisation to other soluble antigens. However, such prevention of acquired immunity could not be demonstrated with skin grafts, though with big doses of 6-mercaptopurine some delay of graft rejection was demonstrable. E. SIMMONS (University of Chicago) reported similar experimental results in rabbits using sublethal irradiation instead of 6-mercaptopurine.

J. W. GOODMAN (Oak Ridge) had shown that when isologous heparinised whole blood was injected into irradiated mice, together with homologous marrow, there was an increased mortality, which did not occur if the blood was irradiated with 75r first. In discussion many made the point that lymphocytes were possibly responsible. G. POPP (Oak Ridge) had shown graded survival of irradiated mice given different amounts of parental marrow, and on the basis of these results suggested that in human subjects too few marrow cells were being given. On a weight-for-weight basis a 70 kg. man should receive about $1{\cdot}05 \times 10^{11}$ cells—far more than is being given at present. Dr. COHEN showed that the interval between sublethal irradiation and time of injection of heterologous bone-marrow was extremely important in determining survival and incidence of secondary disease. If bone-marrow transfusion was delayed until twenty-four hours after irradiation, survival was much

increased. The possibility was raised that some cells responsible for "recognition" might persist in the host for some hours after irradiation.

J. ANDERSON (Texas) reported rapid hæmatological recovery in monkeys given $2{\cdot}5–3{\cdot}5 \times 10^{12}$ bone-marrow cells (isologous) three days after irradiation with 900r.

Dr. SIMMONS and others agreed that the chances of treating systemic tumours successfully by irradiation were poor at present. In rats and mice sterilisation of solid tumours and leukæmic tissue required about 4000r, whereas the present sublethal working limit, except possibly in animals treated with A.E.T. and 5-hydroxytryptamine, was about 1500r, using A.E.T. or marrow transfusion alone. There was still a wide gap to be spanned.

Medicine and the Law

Drink and Diminished Responsibility

DESCRIBED by the prison doctor as a psychopathic personality, a 19-year-old soldier has been found not guilty of murder on the ground of diminished responsibility. He was convicted of manslaughter under the Homicide Act 1957, and sentenced to life imprisonment.

The prisoner was charged with the murder in December, 1958, of a woman whose mutilated body was found in bed. The murder remained unsolved until last November when the police took his fingerprints in connection with another charge. After his arrest, the prisoner made a statement in which he described how he killed the woman; he also referred to attacks on two other women.

Dr. Francis Brisby, principal medical officer at Brixton prison, said that, in his view, the prisoner had a psychopathic personality, which expressed itself in aggressiveness without sufficient cause and in criminal acts which induced no remorse or shame. When he was 15 his headmaster had described him as difficult and precocious. Two years ago he had tried to hang himself. For a year he had been drinking heavily. He had claimed that he never committed any offence except when in drink. The encephalograph findings were abnormal.

Similar evidence was given by Dr. Denis Leigh.

Summing up, Mr. Justice Donovan said that if the jury accepted the evidence that the prisoner was suffering from an abnormality of the mind which substantially impaired his responsibility for the killing, they should find him guilty of manslaughter instead of murder. In his statement to the police, the prisoner had said: "It is when I get drinking I do these things. I am all right when I am sober." If a normal person got drunk or drank to excess and in that condition killed another, it would be no defence to say that he lost his self-control or that his self-control was diminished. The section in the Homicide Act dealing with diminished responsibility was not intended to be, nor was it, a charter for drunkards.

His Lordship continued that two doctors had expressed the view that even if the prisoner did not drink he would still suffer from an abnormality of the mind which substantially impaired his responsibility. "You are not bound by what the doctors have said. If you prefer to accept what the man himself has said, on the grounds that probably he knows best, you are entitled to do on that basis and say guilty of murder."

After the jury had brought in a verdict of manslaughter, his Lordship said that it would be unsafe to impose a sentence of a fixed term of years at the end of which the prisoner would be set free even if he were as dangerous as he was now. The sentence must be one which would enable the authorities to detain him until they were satisfied that he could safely mingle with his fellow creatures once again.

It has for many years been a principle of English law that loss of self-control through drunkenness is not a defence to a criminal charge. The summing-up in this case indicates that there has been no change in this principle as a result of the passing of the Homicide Act. The defence of diminished responsibility under that Act requires some abnormality of mind, and Mr. Justice Donovan was surely right to tell the jury that mere drunkenness did not suffice.

Medical Education

THE NEW AFRICAN SCHOOL

THE Nuffield Foundation has offered £250,000 to the University College of Rhodesia and Nyasaland towards the establishment of a medical school at Salisbury on the lines recommended by the Rhodesia Medical School Planning Committee. This committee [1] has produced two reports, the first [2] of which proposed that a medical school should be part of the University College while the second [3] outlined a curriculum which has attracted much attention and was republished at some length in our columns.[4]

The grant is offered on the understanding that the teaching hospital takes the form of a new multiracial hospital on the University College campus. The planning committee's design for the medical course calls for more integration than is usual between the preclinical and the clinical parts of the course, and by putting the various departments in close proximity the University College has an opportunity to create a medical school which might become a model.

When the new medical school is established, it will initially be an affiliated institution of the University of Birmingham. The planning committee thought that the school should provide its successful students with a qualification which would be widely accepted, rather than with a diploma of only local value. The University of Birmingham agreed to help over this, and the details of its relationship with the African college are now being worked out.

While this relationship continues, students of the new medical school will be admitted to medical degrees of the University of Birmingham, and appointments to the staff of the medical school will be made only in agreement with the university. For its part, the university will ensure that the shaping of the curriculum to meet local needs and opportunities does not affect the standard of the course or of the examinations required. The relationship between the university and the university college will continue until the reputation of the new medical school is so securely established that local degrees which will be widely accepted can be awarded. If thought desirable, the association of the two schools may indeed continue in some form after the university college has become a full university awarding its own degrees in faculties other than medicine.

It is expected that very close personal relations will develop between the medical school at Salisbury and the medical school and the teaching hospital in Birmingham. Staff will be exchanged and joint research undertaken. It is being suggested, for example, that all members of the staff of the medical school at Salisbury should also be supernumerary members of the staff of the appropriate department in the Birmingham medical school. When first appointed, they would spend a period teaching at Birmingham, and at intervals thereafter they would revisit Birmingham to engage, perhaps for a term, in teaching, research, and other departmental duties.

1. The chairman is Mr. Leslie Farrer-Brown and the members Prof. Melville Arnott, Prof. T. H. Davey, Prof. A. D. M. Greenfield, Prof. P. B. Medawar, Dr. Honor Smith, Prof. R. Milnes Walker, and Miss Grace McDonald (secretary).
2. *Cent. Afr. J. Med.* June, 1958.
3. *ibid.* March, 1959.
4. *Lancet*, 1959, i, 929.

In England Now

A Running Commentary by Peripatetic Correspondents

AIR travel is a chancy business at this season. At Rome airport we were told that the plane for Vienna might not be able to leave that night, because of fog at the other end. Until the weather, or the situation, became clearer, would we mind waiting? Dinner perhaps, at the company's expense? Inconvenience much regretted. Finally we boarded the Viscount about 7.30 P.M. There were only 2 of us, and I suggested to my companion that with the two charming, and unemployed, air hostesses we might try to make up a bridge four; but the unenterprising fellow preferred to sleep. We were making, not for Vienna, but for Stuttgart, where we picked up 16 stranded passengers from London. Vienna still being fog-bound, the plane's destination was to be Graz; and there, sure enough, we were decanted into a bus and conveyed to the station, where the airline representative dipped into his pocket and bought 18 first-class tickets to Vienna. At 1.15 A.M., now a rather morose band, we boarded the Balkan express, which fumbled over the 200 kilometres to the capital with no great zeal. Between snatches of sleep I listened to another of the 18 grumbling at the slowness of the train and the woes of all rail travel. But as, at 5.45 A.M., we crept out into the murky capital, I reflected that we should be heartily thankful for this old-world way which was there to serve us when the modern-wonder way had failed.

* * *

I was frightfully excited by the figures. A rough count showed a tremendous difference between the results for the patients who were getting my cherished new treatment and for the control group. Of course, I knew it clinically. But how splendid to prove it by statistics.

I have lately taken a course in statistics, so I knew what to do. I borrowed a calculating-machine for the weekend and roped in my wife—first to keep the children quiet, and then to work the machine for me. She grumbled occasionally and the children grumbled a lot. The cakes burned in the oven and the Sunday joint never got cooked at all. It was an unsatisfactory weekend from the point of view of human relationships and bodily comfort. But I didn't mind: I was much too busy covering sheet after sheet with my calculations.

At least, I didn't mind until Sunday night. Then I minded a lot. My results weren't statistically significant. I just couldn't believe it. The whole world seemed to crash about my ears. Then my wife made some coffee and reminded me soothingly that statistics never proved anything. I recovered sufficiently to write my paper. I became almost pompous about it. "Of course", I wrote with aplomb, "the fact that these results are not statistically significant only confirms our view that it is clinical judgment that counts, and in no way invalidates our findings."

Tomorrow I'll return that damned calculating-machine to its owner and never borrow it again. In future I'm going to trust to clinical judgment during the week and enjoy my week-ends.

* * *

Copying case-histories for the files of the medical school is always somewhat of a problem, for the handwriting of house-physicians needs extensive study and a prolonged acquaintance with medical terms. Each new typist endows us with a series of usually infuriating approximations, but our latest indomitable novitiate, who refused to be beaten by any scribble, commands our respectful admiration. One of her typescripts runs:

"Has been feeling 'dizzy' with his hypolemine drug recently. No pselpilatiars. No spirein. Very shallow complexion. Moderately dyspureic with slight cyarosis. A/B Standing V space 5" fism nidline. No mgms. CHF.=JVP=O". H/S Triple rdtchin. Vesie breathing aneas. V/F nasal and equal parthride. Few asal eceptitatioss. Cheek urine: Alhunan ++ Eurio NAD.

4.5.57. Mouth and throath sowing evidence of incease inflamation reddened day coaked.

5.5.57 Has developed R. parohibis for pencillen and ghrephohugum

9.5.57 Parabibs inversing. Pyrenial. Breathing with markde unspiratory thoidor. Indrowinging of chest. Acceuory unocles of perpuatior archive. Chonic truchihings of arms and head. Rehanded on submit."

Examples of her work are unhappily limited, for we felt it would be a pity to spoil her natural talent by an unduly prolonged acquaintance with medical literature.

* * *

I do not mind being called a stuffed shirt. Television-soaked teenagers can keep their gibes and their jargon. I belong to a different world of visual stimuli, old-fashioned, solid, three-dimensional, flickerless, and mercifully silent. Tucked away behind the stairs is the little room I call my study, with a book-case full of faded medical textbooks and holiday brochures of places we could never afford to go to. A pleasant place for dreams and daydreams, away from the record-player, the radio, and the telly: an English oasis in the yackering desert of show business. If the stuffed shirt fits, I am proud to wear it: but I will not stand for any aspersions on my other stuffed and stuffy friends. A tiptop collection they are, too: all round my study wall. The pike from the edge of the reeds by the island: that was a bitterly cold day for spinning, and Jock Thompson knew how to trade on vanity when he charged me a deal too much for stuffing the thing. The otter pad from that morning when I fell in. The hare pad which was all that was left by the time we plodded up the hill on New Year's Day. The snarling fox mask over the door: he was the one that murdered a couple of dozen of our pullets one October night, and paid for them next day. Then there is the smiling fox by the fireplace. A friendly chap. I think I shall have all my fox masks mounted with their mouths shut in future. They look much more foxy and Corgi-like: much more ready to join in forty winks by the fire. Solid, silent, long-standing friends.

So I was pained to see an exhortation in the agony column of my favourite newspaper to get rid of the rubbish in our attics to some covetous box-number who wants to buy stuffed fish, animal heads, and similar trophies. Just like that it seems so soulless. Can it be that some pools-winner is trying to purchase the priceless heritage of the still waters above our weir, some forecaster to cast his sordid golden lure towards my pike, some eight-draws expert to draw my coverts, to bid his twenty-four against my foxes' points, to back his form against my hare's? And then to have the unpardonable nerve to call them rubbish. And insinuate that I entertain my friends in the attic.

When the time comes for the last tidy-up of my study I shall command my executors to stuff the lot of us all in one box.

* * *

Village shopkeeper: "We're out of friars' balsam, but my daughter always rubs 'Vick' on Johnny's chest when he's poorly . . . you did say it was for Carol, didn't you?"

Puzzled farmer's wife: "No, I said it was for our cow".

* * *

On reading the Registrar General's Statistical Review: Part II Tables, Civil.

In England, Nineteen Fifty Seven,
Many a good soul went to Heaven—
Many a woman, many a maid,
Many a man in many a trade;
And as for the income of them as passed over
Why some was in poverty, some was in clover.

There was some died o' drinkin' and others o' boxin'
And some hadn't taken their tet. antitoxin;
There was some died o' workin' and some had a trauma
(Although thanks to the Union I ain't feared of the former)
And a few had a sickness and some had a tumour
But a terrible lot o' them died of ill-humour.

In England, Nineteen Fifty Seven,
Many a good soul went to Heaven—
Many a Mister, many a Miss
Departed to eternal bliss;
But as to their religious sect,
It didn't make much odds, I expect.

Letters to the Editor

TREATMENT OF INGUINAL HERNIÆ

SIR,—As operations for hernia are about the commonest of all, we must commend the surgeons of St. Thomas's Hospital and the investigators, Mr. Shuttleworth and Mr. Davies, for showing in your issue of Jan. 16 that there is still no cause for complacency in the treatment of inguinal hernia. Few of those who embarked on the primary repairs of the 204 indirect and 94 direct hernias would have believed that 1 in 7 and 1 in 6 respectively would recur.

One of the more solemn thoughts in connection with operations for hernia is that recurrences of even the third and fourth generation can be permanently repaired by a well-planned soundly executed operation; and all must agree with the authors that it is " difficult to escape the conclusion that the remarkable results obtained on recurrent herniæ are partly related to the extra care that is called forth by these herniæ ". Doubtless the more experienced operators would also be called forth for the recurrent herniæ, and though we are all capable of making a botch of things from time to time, care, knowledge, and experience evidently help. So much for the human factors.

It seems that the method may also be a help, and Mr. Shuttleworth and Mr. Davies give general commendation to the nylon darn technique; for the 18 recurrent herniæ repaired by this method with no recurrence seem to be top of the bill, and results with nylon darns appear to be unbettered for those primary repairs more extensively used. Has nylon any special properties to commend it in addition to it being easy to insert? I believe it has, for when it is used as a thick single strand it retains tensile strength even after long periods of implantation in the tissues. Linen, silk, and cotton sutures and also braided nylon, floss nylon, and any preparation of nylon in the form of fine weave all have their tensile strength reduced to nil after six months in the tissues. But the thick no. 7 single strand of nylon retains at least two-thirds (and probably more) of its tensile strength after eleven years in situ, and though the tissues do have some effect upon all implanted nylon the thickness of the strand is sufficient to stand up to the weakening influence of the body's chemicals. Thick strands darned into a mesh and lying in the fibrous tissue formed in and around a darn continue to act as part of the buttress and are especially protective during high strains. The evidence in support of these facts has been submitted elsewhere for publication and calls for no elaboration here.

Those who may wish to try nylon as a darn in the inguinal canal should not be put off by talk of sinuses. When nylon is used in closing incisions higher up in the abdomen after operations on the alimentary tract, sinuses undoubtedly occur at times; but the incidence of sinuses arising from nylon buried in the depths of the inguinal canal, even in patients with strangulation, is extremely low, and is far outweighed by the advantages. Almost all sinuses after infection or hæmatoma will close if the infection is treated by antibiotic and the sinus by patience. Catgut does well in closing the external oblique, leaving the area pliant and the darn impalpable.

The Radcliffe Infirmary, Oxford. G. E. MOLONEY.

ESTIMATION OF BLOOD-ALCOHOL BY BREATH ANALYSIS

SIR,—I am a little perturbed by the rumour that the 'Breathalyzer' is to be used as a means of estimating blood-alcohol. In fact, it measures the amount of alcohol in an aliquot of expired gas. It is probable that in a healthy resting subject the vapour pressure of alcohol present in his alveolar gas will be in equilibrium with that in the arterial blood. For many years now it has been realised that a sample of this gas may be obtained only from trained healthy subjects; such a sample cannot be obtained from untrained subjects whose lungs are at all emphysematous. Moreover, the alcohol concentration in the expired gas of a given subject will depend critically on the rate of pulmonary ventilation; it should be easy for a partially intoxicated subject to hyperventilate for a minute or two before giving the required sample and thus halve the concentration of alcohol in his lungs. The relation between the alcohol in expired gas and in the tissues, although explicable, is not at all simple. I foresee many a happy hour spent in court by medical experts reconciling the results given by the breathalyzer with the facts of a case as presented by the prosecution or defence.

Institute of Diseases of the Chest, London, S.W.1. F. J. PRIME.

PULMONARY DIFFUSING CAPACITY

SIR,—The single-breath method of measuring the pulmonary diffusing capacity for carbon monoxide which has been modified and developed by Forster et al.[1 2] has not fared well in your recent issues. Firstly, Professor Melville Arnott (Jan. 2) refers to Bates and Christie [3] who did not use the test and, secondly, Dr. Jones and Mr. Meade (Jan. 9) have set about improving the test on an erroneous assumption. The improvement depends on the recalculation of the breath-holding time to allow for the time taken to deliver the alveolar sample, and the assumption is that this is important because the alveolar sample is large and consists of several litres.

The misunderstanding has undoubtedly arisen from the description of the method by Ogilvie, Forster, and others,[2] who state that all the expirate is collected after the first litre, which is rejected because it is contaminated with dead-space gas. However, it is quite clear from their later discussion about different portions of expired alveolar gas, that only a small sample is required for gas analysis (approximately 300 ml.) and that this is taken from the second litre. From personal experience of making many measurements with Forster, I can state that in practice the collecting period is always kept as short as possible.

It is doubtful if it is necessary to adopt the modified method for measuring the " effective " time of breath-holding except in patients suffering from severe impairment of the expiratory flow rate. Since the problem then is to get a sample large enough for gas analysis, because of air trapping due to forced expiration, the error arising from large changes in alveolar volume during expiration, which is also mentioned by Jones and Meade, becomes unimportant.

Department of Pharmacology and Therapeutics, Queen's College, Dundee. R. S. MCNEILL.

SIR,—Dr. Jones and Mr. Meade have put forward an ingenious and convincing explanation for the fall in pulmonary diffusing capacity which has been observed during breath-holding.[1 2]

It seems that this fall is an artefact and can be abolished by timing the breath-holding periods from the start of inspiration to the midpoint in time (instead of the start) of sample collection, and then subtracting $^3/_{10}$ of the inspiratory time. It is questionable, however, whether the errors which they seek to overcome are either consistent or great enough to justify adopting their more complicated methods of timing and collection for routine clinical purposes.

1. Forster, R. E., Fowler, W. S., Bates, D. V., Van Lingen, B. *J. clin. Invest.* 1954, **33**, 1135.
2. Ogilvie, C. M., Forster, R. E., Blakemore, W. S., Morton, J. W. *ibid.* 1957, **36**, 1.
3. Bates, D. V., Christie, R. V. *Clin. Sci.* 1950, **9**, 17.

My colleagues and I [2] were able to collect adequate samples from each of our 28 untrained subjects in from 1 to 2 seconds. In this group, Jones and Meade's timing corrections would have produced variations of about 5% in calculated diffusing capacity. Providing that the subject is told to expire with all his might, he will add little to the sample after 2 or 3 seconds, although, in emphysematous patients especially, a noisy expiratory effort may continue for several seconds more. When sample collection is continued beyond this initial period of 2 or 3 seconds, an error is more likely to arise if, as suggested by Jones and Meade, a fixed proportion of the total collection time is counted as time available for diffusion. On the other hand, when the sample is collected within 2 or 3 seconds, these timing corrections seem scarcely worth while.

I do not think therefore that the proposed modifications to the breath-holding test are necessary for ordinary clinical purposes, but I would like to congratulate Dr. Jones and Mr. Meade on their solution to a problem which has mystified workers in this field for a number of years.

Liverpool Stanley Hospital,
Stanley Road, Liverpool. COLIN OGILVIE.

C-REACTIVE PROTEIN IN BURNS

SIR,—Your stimulating leading article of Jan. 16 on the still very obscure and controversial subject of toxæmia of burns encourages me to recount some interesting observations which have been made on patients from our burns unit.

It occurred to us that it would be worth studying the behaviour of C-reactive protein (C.R.P.) in the blood of patients with burns, in the hope that serial quantitative estimations may provide a useful guide in the assessment and prognosis. With this object in view a new technique for the qualitative and quantitative estimation of C.R.P. has been developed in our laboratory. It is based on immunodiffusion on cellulose acetate and permits the test to be performed on serum or on whole blood from a finger prick, thus enabling frequent serial estimations to be carried out even on children and severely burnt patients.

We have carried out a series of investigations on patients with burns of widely different area, depth, and clinical severity. In about 40 cases so far investigated we have found that the presence and the level of C.R.P. in the blood appears to be closely correlated to the extent, depth, and severity of the burns. Curves obtained from several estimations of C.R.P. follow quite closely the progress of tissue breakdown and also the clinical state of the patient.

A certain minimal amount of tissue damage has to be present before the C.R.P. can be detected. With the same surface area involved, full skin loss produces a much higher level of C.R.P. than a superficial burn. In other words, the greater the tissue damage the higher the C.R.P. level. The presence of C.R.P. is detected within 24 hours from the time of the burn, sometimes even within 12–16 hours. In moderately severe, uncomplicated cases progressing towards recovery the C.R.P. level rises steadily and reaches a peak in about 5–7 days. With uneventful recovery and satisfactory healing, the C.R.P. level drops steadily until no more C.R.P. can be detected. In milder cases the increase of the C.R.P. level may last only a few days.

Complications involving further tissue necrosis, or acute inflammation with infection, may cause a secondary rise in the C.R.P. level, which may precede overt clinical manifestations, and thus indicate some unsuspected tissue damage. In severe cases the C.R.P. level rises steeply until a high titre is reached. Recovery is accompanied by a steady fall of the C.R.P. level. In fatal cases an abrupt drop was sometimes observed in the terminal stage. This drop may coincide with the hypothermic phase. In very severe burns, particularly in old patients, the rise in the C.R.P. level may not be dramatic and will reach only a comparatively low level. This might conceivably be associated with an overwhelming metabolic failure or, if death occurs in the first few days, the peak values may not have been reached.

The results so far obtained indicate that the estimations of C.R.P. may be of considerable value in the assessment of the severity of burns, and of the efficacy of therapeutic measures (be they conservative or surgical), and may also be of some help in the prognosis. The subject is now being investigated in detail, more material is being collected, and after a significant number of cases have been investigated it is intended to publish a full report.

Queen Mary's Hospital,
Roehampton, London, S.W.15. J. KOHN.

WITHHOLDING OF SICKNESS BENEFIT

SIR,—It was interesting to read that another medical man (Jan. 23, p. 228) had suffered the same treatment by the National Insurance set-up as myself. Dr. Edelston's prediction that to go on in an attempt to obtain redress is a waste of time and a foregone conclusion is only too true.

After the first refusal I elected to go before a "tribunal" over my claim. There were three members, and the chairman's opening gambit was that "if they leaned over backwards" there was nothing they could do about the matter. One's immediate reaction was to say, Why waste my time and yours then? In the letter I received a few days later informing me that the tribunal had turned down my appeal was a notice that I could have my claim sent to the Commissioner in London. This I did, and after some 3–4 months back came a long screed putting the points of my case, but of course ending with a refusal to allow my claim; so, after all this, we were where we started.

The whole thing is so unjust that I feel it needs thoroughly airing, and should be taken up in an attempt to get such infamous rules amended.

Lenham, Kent. W. A. HERVEY.

AN ILLNESS OF INFECTION IN CHICKENPOX

SIR,—Dr. Partington (Jan. 16) has I see resurrected the suggestion made by my late chief, Dr. Edward Goodall, that an "illness of infection" occurs in measles, and he now puts forward his reasons for believing that a similar illness may occur in chickenpox as well.

If an "illness of infection" actually occurs within a day or two of infection with measles, then it can only mean that the body defences have been effectively challenged by a score or two of virus particles to produce a vigorous defence reaction but one that is curiously lopsided. For though the febrile component is well marked the antibody factories remain remarkably inactive. Otherwise the virus, when in due course it had penetrated its target cells, replicated a millionfold, and burst into the bloodstream, would find itself, like the variola virus in a smallpox contact vaccinated a few days after exposure, confronted with a flood of antibodies. But that does not happen here; the measles virus is in no way impeded and produces an attack of normal severity. If the "illness of infection" were followed by an attenuated attack—or sometimes none at all—it might be credible, but as things are it would seem to be quite purposeless. It is my general impression that the defence mechanisms of the body do not indulge in purposeless reactions.

However, leaving theory aside, I remember that when Goodall first published his views I was then one of his very new junior assistants and I was naturally anxious to verify his observations. Scope was abundant, because in those days with large open wards measles intrusion was common and exasperating. Before convalescent serum became available, two or three cases might occur every fortnight until the supply of susceptibles ran out; meantime valuable beds were inactivated for weeks on end. Diphtheria wards offered a particularly good field for observation as the disease was largely afebrile and the patients, although relatively long-stay, were kept under the strictest observation in view of possible complications. But I

proved impossible to correlate the occasional febrile episode that occurred with the subsequent fate of the patients. The vast majority developed measles without any sign, while those who exhibited what might be properly regarded as an "illness of infection" did not develop it at all, or developed it at the next crop but one. It was indeed impossible to confirm Goodall's theory, and this too was the experience of my colleagues.

In the circumstances, the concept of an "illness of infection" is one which, in common with most experienced observers, I find myself unable to accept, and I would suggest that febrile episodes in the course of an incubation period should be thoroughly investigated for some other pathological basis. Otherwise one may be doing a serious disservice to one's patient.

South Middlesex Hospital, Isleworth. G. E. BREEN.

TRETAMINE IN THE TREATMENT OF INOPERABLE LUNG CANCER

SIR,—My communication of Jan. 23 on this subject has resulted in a quite unexpected amount of publicity and correspondence. It is clear that some have interpreted the figures incorrectly and I should like to restate these in another form lest many have been so misled. 43 patients were included. Tretamine had no helpful action on 13. In 30 cases some subjective improvement was noted. This was meant to imply that after the nausea had subsided they felt better, but in 20 there was no objective evidence of a favourable response.

10 cases showed shrinkage of the tumours. In the 4 described in detail and in the 3 who died of hæmorrhage, these changes were observed radiologically. The other 3 of these 10 cases (referred to in paragraph seven of the report as "The remaining patients") had metastatic disease which was observed clinically to regress with relief of pain and a reduction in tumour bulk.

Of the whole series there are 7 survivors, including the 4 referred to in detail.

I very much regret that this paper, prepared entirely by myself and for which I accept full responsibility, has been so laid out as to be open to misinterpretation, and has thereby given undue hope or optimism to many people.

Baguley Hospital, Manchester. GORDON D. JACK.

CHEMOTHERAPY OF MALIGNANT DISEASE

SIR,—Your leading article of Jan. 23 referred to the failure of very high concentrations of chemotherapeutic agents to "cure" certain tumours. It is possible, however, that the first chemotherapeutic "cures", or at least the first prolonged remissions have already been obtained. I refer to the treatment of widely metastasised trophoblastic tumours by anti-metabolite substances. Follow-up of such cases by Hertz [1,2] in the U.S.A. extends up to four years, and similar cases have been followed without evidence of recurrence for eighteen months in this country.

The success so far achieved with these tumours is partly due to the invaluable guide to therapy which is provided by sensitive, quantitative methods of assay of gonadotrophin excretion. Gonadotrophin excretion appears to be a reliable guide to the amount of viable tumour tissue, and the well-recognised need for a similar guide to therapy in other forms of cancer is underlined. Whilst it does not follow that non-trophoblastic tumours will behave in the same way as those of trophoblastic tissue, it would be unwise to ignore the experience gained from treatment of the latter.

For instance, widely metastasised choriocarcinoma has responded at least as well to moderately high plateau levels of anti-metabolites sustained for several days, as to much higher peak levels sustained for short periods. Perhaps the most important observation from the treatment of these tumours relates to the futility of clinical and radiological evidence of remission as a guide to the need for further therapy. Thus clinical and radiological remission often follows after one or two courses of treatment, whereas complete and sustained hormonal remissions are usually obtained only after seven to twelve courses of treatment extended over periods of four to six months.

It seems likely that as a result of recent observations there will be increasing use of hormones, hypophysectomy, and the expanding range of chemotherapeutic substances in the treatment of cancer. The widespread and haphazard use of these forms of treatment, however well-intentioned, can add little or nothing to our present knowledge. The necessity for well-planned trials of these various methods used alone and in combination in a wide range of tumours is all too obvious, and it can be assumed that many clinical trials are already under way. Need it be said that because of the sheer size of the problem there is equal need for some coordination of these trials, if effort and time are not to be dissipated.

St. Mary's Hospital, London, W.2. K. D. BAGSHAWE.

B.C.G. VACCINATION

SIR,—Your leading article last week puts into proper perspective a subject which has been surrounded by much turgid and irrational thinking in recent years.

If, however, tuberculosis is to be controlled or eradicated, a curious gap in our knowledge and armamentarium must be filled. I refer to the care of the children who are tuberculin-positive.

So far great efforts have been directed towards protecting the tuberculin-negative groups by B.C.G. vaccination. With the fall in incidence of tuberculosis and consequent rise in the proportion of negative reactors, the law of diminishing returns comes into operation and the value of mass B.C.G. vaccination diminishes. The group of tuberculin-positive reactors then assumes much more importance, because it is from this group that future cases will arise in the vulnerable periods of adolescence and early adult life.

If a positive tuberculin test in children means anything, it means infection by the tubercle bacillus, and not too long ago. In all probability such infection will confer as much immunity as B.C.G. vaccination. It would therefore seem reasonable that these children should be treated as though they had primary tuberculosis, and given appropriate therapy. This must result in a fall in the incidence of post-primary cases arising in later life from this group, and break one chain of infection. This would lead to an even more rapid decline in incidence and less need for mass B.C.G. vaccination.

The greatest danger that arises from the use of mass B.C.G. vaccination is that it renders ineffectual the tuberculin test as a means of identifying infected persons, and although this may be diminished by the establishment of a central registry, it would seem more important that tuberculin testing should continue to be used in identifying chains of infection, especially those arising from the largest pool of cases apart from immigrants—that is, the older age-groups. These groups have been thrown into relief by the changing pattern in recent years, and can only be dealt with by more intensive case-finding and clinical methods.

Effective drug therapy for tuberculosis has now been in use for at least ten years, and perhaps those with most experience could tell us whether the dangers and difficulties of drug therapy would outweigh the benefits to be obtained from its application to children who have become tuberculin-positive from natural infection.

Dungannon, Co. Tyrone. T. G. MILLIKEN.

1. Hertz, R., Bergenstal, D. M., Lipsett, M. B., Price, E. B., Hilbish, T. F. *J. Amer. med. Ass.* 1958, **168**, 845.
2. Hertz, R. Personal communication.

HOTELS OR HOSPITALS?

SIR,—The stimulating articles in your issue of Jan. 9 by Mr. Stallworthy (p. 103) and your peripatetic correspondent (p. 109) are timely. Many of our present troubles are due to a perpetuation of medical thoughts and actions common before the N.H.S. began, but still regarded as sacrosanct.

There are still too many small hospitals of less than 100 beds, dissipating medical and nursing manpower. This is a small country: most patients are really not so far from large towns and the larger hospitals, which could well be made larger with the money saved in closing small and inefficient units.

Road and other accidents are surely going to increase. Many are treated in small general hospitals ill equipped to deal with them. A nationwide accident service is urgently needed, perhaps based on hospitals such as the Birmingham Accident Hospital. Again, local medical, if not lay, sentiments must be overcome.

Long waiting-lists are commonly held responsible for delay in admission. Not enough thought is being given to why some lists are longer than others, not only in different specialties but in the same specialty in different areas. Again, little effort is made to revise lists at regular intervals. Who should do this? Certainly not lay record officers. It would be revealing to know how many patients on particular lists have moved or been treated elsewhere; who have died, who will have refused treatment, and, most important, who may not need treatment after all. This type of investigation again depends largely on medical cooperation and would apply to such conditions as " tonsils ", chronic appendicitis, and D. & C.

As for the special problems of the fever hospital, it is true that many have empty beds, but when they are needed they are needed in a hurry. Epidemics are unpredictable, and it is wishful thinking to say that they cannot happen here. Surely the best analogy is the Fire Service, which equally ties up valuable manpower, material, and space.

It is time that a more rational and less emotional approach to the value of good medical administration was adopted by all doctors. Maybe this is a glimmer on the horizon.

Chadwell Heath Hospital, Romford, Essex. I. M. LIBRACH

TREATMENT OF GALACTOSÆMIA

SIR,—In reply to the letter from Dr. Schwarz and his colleagues (Dec. 19) we wish to apologise for an error which was overlooked in our letter of Nov. 14. Galactose-1-phosphate was actually expressed as micromoles not as microgrammes. If the values quoted in our letter are transferred to microgrammes it will be seen that the two sets of normals are in agreement.

Their suggestion that soya meal should not be used until it is " proved " safe surely would prevent its being used at all. Strict proof that stachyose is not digested by the human infant can at present be obtained only by giving it to a galactosæmic infant and showing that this does not lead to an accumulation of galactose-1-phosphate in the erythrocytes. Since stachyose and other compounds containing galactose occur in various other foods besides soya which are used in the treatment of galactosæmia a considerable amount of testing of these different compounds would have to be carried out, and in view of the limited number of galactosæmic babies available such testing might well take several years to complete. In the meantime cases of galactosæmia are urgently needing treatment, and soya preparations may surely play a useful part as long as they are found not to cause an accumulation of galactose-1-phosphate in the erythrocytes.

While the few cases we have so far treated with soya preparations cannot be taken to prove the safety of soya, such evidence as we have been able to get supports the belief that galactose is not liberated in sufficient amount to cause a measurable increase in the erythrocyte galactose-1-phosphate. Clinical observations unsupported by chemical tests cannot on a short-term basis be accepted as proof of either danger or safety. The failure to gain weight (apparently due to gastro-intestinal disturbances) shown during a short period in the single case reported by Dr. Schwarz and his colleagues need not have been due to galactose liberation. We have seen a similar picture frequently when very young infants are placed abruptly on a synthetic diet. If the new diet is introduced gradually over several days intolerance can be avoided.

The addition of different foods to the diet of a galactosæmic infant may introduce a possible source of danger, since many baby foods contain appreciable amounts of lactose or other compounds of galactose. It is necessary to discover what foods are galactose-free. Jones and Leak [1] have given some indications of this in a recent paper, and we are now starting a study of the galactose content of weaning foods which we hope may give useful results.

The Hospital for Sick Children, Great Ormond Street, London, W.C.1. W. W. PAYNE.
University College Hospital Medical School, London, W.C.1. T. A. J. PRANKERD.
Vegetarian Nutritional Research Centre, Stanborough School, Garston, Watford, Herts. FRANK WOKES.

***At Dr. Payne's suggestion we published a correction about the galactose-1-phosphate levels in our issue of Nov. 28, but we failed to draw it to the notice of Dr. Schwarz and his colleagues before publishing their letter. We apologise to all concerned for our part in this misunderstanding.—ED. L.

DENTAL DRILLS

SIR,—In your leading article of Jan. 2 the possible risks to an operator using the new high-speed air-turbine instrument are discussed. As you say, such risks may be caused by particles of tooth and old filling material propelled into the air by the blast of the turbine exhaust and by oil used in lubricating the turbine, which may be entrained in droplet form with the air-supply.

Last year, at the request of Dr. W. G. Senior, chief dental officer to the Ministry of Health, a preliminary investigation was carried out in this department on the environmental problems involved. An 'Alston' drill was used. In this instrument, the turbine is powered by an airstream which first passes across a vegetable-oil drip feed, while a secondary air-supply directs a jet of water on to the head of the bur. At an operating air pressure of 40 lb. per sq. in. the turbine speed was found to be approximately 260,000 r.p.m. under no-load conditions.

We did not measure the sound output, but a crystal pick-up, making mechanical contact with the turbine head, off load, showed a fundamental vibration of 4400 cycles per second, with some distortion, but not enough to suggest the presence of a high percentage of harmonics. Thus, the major sound emission can be expected at this frequency.

In order to study atmospheric contamination arising from drilling, four teeth, mounted in a cavity simulating the human mouth, were drilled continuously for 30 minutes, with an oil flow of 33 drops per minute, and a water flow of 2·6 ml. per min. An air sample, taken at a point one foot in front of the " mouth " and six inches above it, showed an average concentration of 1·3 mg. oil per cubic metre of air. Microscopic examination of a cascade impactor sample showed that the greater mass of both the oil and particulate matter was trapped in drops of water larger than would usually be considered " respirable ". A second sample, taken during ten minutes of drilling, showed a calcium concentration from the tooth particles of 100 μg. per cubic metre of air. In actual practice the drill would not be used for as long as ten minutes, so that the concentrations obtained would be lower. It was concluded from the experiment that there was little risk to the operator

1. Jones, N. L., Leak, D. *Arch. Dis. Childh.* 1959, **34**, 307.

from the inhalation of oil or tooth particles under these circumstances.

However, we would endorse the statement in your article that mineral oils used for lubricating purposes might provide a risk, mainly of lipoid pneumonia, and we wish to stress that the above remarks apply only to the use of a vegetable oil. The question also arises of bacterial contamination by the blast of air from the turbine, but we have no observations as yet on this point.

We have recently been informed that some dental surgeons have experienced irritation of the eyes and respiratory tract following the use of an air-turbine drill, and we would be interested to hear from others who have experienced any untoward effects.

Department for Research in Industrial Medicine, Medical Research Council, The London Hospital, London, E.1 — G. KAZANTZIS, E. KING.

EFFECT OF BEER ON BLOOD FIBRINOLYTIC ACTIVITY

SIR,—The appetising experiments of Dr. Fearnley and his colleagues (Jan. 23) suggest that drinking ten to forty ounces of alcoholic beverages reduces fibrinolytic activity, whereas two ounces does not. Is the lysis-time similarly prolonged by swallowing ten to forty ounces of water, or even air?

St. Thomas's Hospital, London, S.E.1. — G. I. C. INGRAM.

SKIN CHANGES IN HYPOCALCÆMIA

SIR,—Professor Dent and Dr. Garretts (Jan. 16) state that in their cases with hypocalcæmia "it is the lowered calcium level that is the main cause of the skin lesions". Observations of a similar patient with idiopathic steatorrhœa and erythrodermia make me believe that this statement is an oversimplification of the facts as far as idiopathic steatorrhœa is concerned.

In July, 1954, a male of 22 was diagnosed by Dr. Kenneth Perry as idiopathic steatorrhœa with exfoliative dermatitis. His rash had begun some 8 years before and had become generalised. For 7 months there had been progressive weakness and pallor. He was emaciated, pale, and almost bald. There was generalised erythrodermia and dusky brown pigmentation of the skin, with ectropion, and maceration and fissuring of the flexures. The nails were rough and thickened. There were retinal hæmorrhages and exudates. Chvostek's sign was positive. The hæmoglobin was 15% (2·2 g. per 100 ml.): red cells 1,060,000, leucocytes 2400 per c.mm.: plasma-protein 6·0 g. per 100 ml. (plasma albumin 3·9, globulin 2·1). Serum-calcium 6·6, inorganic phosphorus 4·8 mg. per 100 ml.: acid-phosphatase 0·6 units and alkaline-phosphatase 10 units. The liver biopsy showed an excess of hæmosiderin pigment mainly in the Kupffer cells, and also to a slight extent in parenchymal cells and portal tracts. Liver-function tests and blood-urea were normal. Barium meal and follow-through showed "steatorrhœa pattern" in small intestine. The sugar-tolerance curve was flat.

After treatment by blood-transfusion, folic acid, iron, vitamins, calcium lactate, calciferol, and a high-protein gluten-free diet, his general condition improved greatly and the anæmia and disturbance of serum-calcium were corrected, and have remained normal ever since. He has obtained work, maintaining television sets.

Since June, 1959, his treatment has consisted only of a gluten-free diet. In September, 1959, his serum-calcium was 10·4, inorganic phosphorus 3·6 mg. per 100 ml., and hæmoglobin 94% (13·8 g. per 100 ml.).

Unfortunately the condition of his skin has not improved pari passu with the great improvement in his general condition. After an initial improvement in texture, diminution of pigmentation and exfoliation, the skin has remained for some 5 years red and finely peeling, and with intermittent ulceration of his pachydermatous lymphœdematous ankles.

I think it is right to regard his erythrodermia as having been caused by a gross and broad nutritional deficiency—of protein, vitamins, and iron, as well as of calcium. The failure of his skin to recover conspicuously may be due to irreversible damage caused by the great severity and duration of his disease; but I attribute the degree of improvement that has occurred to the correction of his protein, vitamin, iron, and calcium deficiency and to the dietary gluten restrictions, but not to the correction of his calcium deficiency alone.

London, W.1. — BRIAN RUSSELL.

INTESTINAL ABSORPTION OF VITAMIN B_{12} AND THE B_{12} COENZYMES

SIR,—Dr. Wasserman and his associates [1] recently commented on the paper by Reizenstein and Nyberg [2] and mentioned some experiments with the 5,6-dimethylbenziminazolyl cobamide coenzyme (B_{12Co}) isolated by Barker's group. In this connection some of our experiments with non-labelled B_{12Co}* may be of interest:

(1) Four patients with genuine pernicious anæmia were submitted to Schilling tests in which intrinsic factor (20 ml. of gastric juice) was given with 2μg. of radiovitamin B_{12}. Before or after the mixing of the two, 15 μg. of non-labelled B_{12} or B_{12Co} was added. The object was to study whether or not one of the two substances (B_{12} and B_{12Co}) was absorbed preferentially in the presence of the other (cf. Bishop et al.[3]). Compared with non-labelled B_{12}, B_{12Co} had an equal or slightly weaker inhibitory effect on the absorption (urinary excretion) of radiovitamin B_{12} under the conditions used. In other words, B_{12} and B_{12Co} diluted the isotope in about the same way. This fits in with the finding [1] in studies with liver homogenates that B_{12} and B_{12Co} compete in a 1 : 1 ratio.

(2) The binding of B_{12} and B_{12Co} to gastric juice was studied in vitro. If B_{12Co} was added first and radioactive B_{12} afterwards, the binding sites were occupied by B_{12Co} and the subsequently added radiovitamin B_{12} was able to displace B_{12Co} from some 30% of the binding sites. Under the same conditions B_{12Co} displaces about 10% of previously bound radioactive B_{12}. Thus the affinity of B_{12} for the binding sites is somewhat greater than that of B_{12Co}. In addition, the same electrophoretic fractions of gastric juice were found to bind both substances. In these experiments binding was assayed with both exhaustive dialysis and adsorption of free B_{12} to resting bacterial cells. Since B_{12Co} is light-sensitive all experiments were performed under as dark conditions as possible.

Thus, our preliminary studies indicate that B_{12} and B_{12Co} behave in roughly the same fashion. In view of the indirect way we studied B_{12Co} (no radioactive B_{12Co} was available to us), we do not know whether it is absorbed better than B_{12}. Supposing both compounds are taken up by the same acceptor mechanism in the intestinal wall, preferential absorption of one would be expected to inhibit the absorption of the other. However, in our experiments B_{12Co} did not inhibit the absorption of radioactive B_{12} even as much as non-labelled B_{12} did. On the other hand, using radioactive B_{12Co} Dr. Wasserman and his associates [1] found that the absorption of B_{12Co} is not so dependent on intrinsic factor as that of vitamin B_{12}. This may perhaps be related to the weaker binding affinity of intrinsic factor preparations for B_{12Co}.

Minerva Foundation Institute for Medical Research, Helsinki, Finland. — RALPH GRÄSBECK, FRED BJÖRKSTÉN.

1. Wasserman, L. R., Estren, S., Brody, E., Herbert, V. *Lancet*, Jan. 16, 1960, p. 173.
2. Reizenstein, P. G., Nyberg, W. *ibid.* 1959, ii, 248.
3. Bishop, R. C., Toporek, M., Nelson, N. A., Bethell, F. H. *J. Lab. clin. med.* 1955, **46**, 796.

* Supplied by Dr. H. A. Barker, Department of Biochemistry, University of California, Berkeley 4, California.

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—In view of the comments that my letter of Jan. 2 provoked, may I be allowed to enlarge on certain aspects?

In reply to Mr. Murley (Jan. 9), there were 1752 cases of cavernous angiomas or nævi and 814 cases were given superficial X-ray therapy. No attempt was made to analyse this series in detail, for the paper quoted would have been as long as the original article by Dr. Simpson (Dec. 12).

My letter was not even a criterion of this excellently produced article, but merely to call attention to another viewpoint. Do cavernous nævi across the Atlantic behave so differently from those in this country? I would consider American documentation quite our equal.

I entirely agree with Dr. Sneddon (Jan. 16) that it is far easier to treat than to adopt an attitude of masterly inactivity, but there is surely some place for a mother's peace of mind to know that something is being done and that the disfigurement will go from baby in the minimum of time.

My practice has been to treat all such lesions with thorium X varnish (2500 e.s.u. per ml.) once per month, and only where there was increase in size or failure to satisfy the parents, resort to superficial X-ray therapy.

In reply to Dr. Moynahan (Jan. 23) none of the cases given superficial X-ray treatment was given more than 1200r units, and the majority reacted satisfactorily to smaller doses.

I, too, examined many troops in the past war, although I could not claim to have seen 100,000 men, unless it was a march past. I admit I too saw no evidence of cavernous nævi, but this is easily explained because I was not looking for signs of them, and the same applies to Dr. Moynahan.

I see their evidence now because I am looking for them, and can only offer Dr. Moynahan an invitation to spend a pleasant weekend with me at the seaside and show him a few, commencing with one of my own sons.

This brings me to another point. Is it a good treatment to leave a child up to the age of 5 or 7 with a disfiguring blemish even if it is going to disappear spontaneously? Psychiatrists would have very strong views on this.

I am convinced that superficial X-ray treatment reduces to a minimum the cases of spontaneous ulceration, and of course it is the subsequent scarring of these one sees later in life.

In my own child, contrary to my judgment, I followed the advice of no treatment, spontaneous ulceration occurred, and there is certainly no maternal satisfaction, which I would remind Dr. Moynahan was the criterion of cure. Does he produce this by doing nothing? I cannot believe it.

May I remind readers that no dermatologist can have seen more children than Dr. R. T. Brain, of Great Ormond Street, and it has always been his practice to give superficial X-ray therapy where necessary. In a reported series of 614 cases [1] 147 lesions were untreated and they cleared up nearly as well, although not so quickly.

I can think of many patients over the past 15 years who were dissatisfied with the rate of progress, but ready to wait patiently. Very few would have been satisfied to sit back and see nothing done, and moreover the vast majority of family practitioners are relieved to know that these cases are being taken in hand.

It can never be the genuine view of any that nothing active must be done, for several of the cavernous nævi in Dr. Millington's and my series interfered with feeding, breathing, and vision. Do our advocates of no treatment employ pipette or tube feeding, let the respiratory embarrassment remain, or allow the baby to grow up with monocular vision?

I am grateful to Mr. Denis Browne for the reproductions accompanying his letter of Jan. 30. These illustrate very adequately the type of angioma that leaves persistent deformity.

I am also grateful to Dr. Brian Russell (Jan. 30) for his excellent series, but here again I consider he supports our view. If this baby had been his own child would he be prepared to just look at it for 6 years and do nothing? Would he be proud as father and dermatologist of his disfigured offspring? What about the mother's wishes, and I very much doubt if the last three blank spaces will show an absolutely normal lip—when he starts school his playmates will pull it and upset him.

One of my surgical colleagues has just told me of a case that recently came under his care and was referred by him to the Royal Marsden Hospital. The diagnosis was carcinoma of the thyroid and alleged to have followed X-ray therapy for a nævus, but he took the trouble to inquire exactly concerning this and found to his surprise that only thorium-X varnish had been used and no X-ray treatment given. I imagine even the die-hards would hesitate to blame this form of radioactivity.

Hove. E. COLIN-JONES.

SIR,—I agree with Dr. Ray Bettley (Jan. 23) that the application of carbon-dioxide snow for 15 seconds will abolish a small superficial lesion, usually with a good cosmetic result, but unfortunately, especially on the face, an unpleasant and permanent dead-white scar occasionally results. This is very uncommon after short applications, but I have seen it several times and am therefore reluctant to use such treatment. It is much more debatable whether snow will "gradually improve all the rest". It is usually possible to decolorise the surface, but the deeper parts of thick lesions may persist, and accidents can happen.

My teacher, Dr. Sydney Thomson, once advised me that the first application of snow to a cavernous hæmangioma should never be for more than 5 seconds, with minimal pressure, in case of idiosyncrasy. Although I now seldom use such treatment, I was recently prevailed upon by an anxious mother and a persuasive doctor to apply snow for 5 seconds to part of a lesion covering an infant's patella. The resulting sloughing ulcer took six months to heal, after which the child required admission to hospital for manipulation before it could be induced to move its knee. The end result was an unsightly scar in and around the treated area with spontaneous disappearance elsewhere.

It is because of cases of this type, admittedly unusual, that I cannot agree that such treatment is "so simple, safe and effective that one wonders why anyone should wish to withhold it". This is, in effect, what Dr. Colin-Jones and others have said of radiotherapy, yet most of us prefer to avoid it in so benign a condition, however rare unfortunate results may be.

Hythe, Kent. DENIS SHARVILL.

SIR,—This very interesting discussion may be a vindication for "clinical impressions" as compared with statistics, for the value of which we have the opinion of Benjamin Disraeli. I have read all the contributions with reasonable care, but nowhere can I find mention of the possibility of the "cavernous hæmangiomata" becoming malignant in after years. This outcome must be rare, but it does happen, and is therefore a point in favour, perhaps, of operation. I have seen one such case, in a girl aged three years, who had her "cavernous hæmangioma" removed at operation, only to succumb to a sarcoma primary in the operation scar, about the age of fifteen

1. Brain, R. T., Calnan, C. D. *Brit. J. Derm.* 1952, **64**, 147.

The obvious course seems to be, " keep the patient under observation " for many years if possible. One advantage of operation is that sections can be studied; much can be learnt from careful study.

St. Margaret's Hospital, Epping. FRANK MARSH.

SIR,—Will you please allow me to thank all of your correspondents who have shown such an interest in my paper on this subject and to make a few comments?

My aim was to provide more factual information, in rather more detail than had been published before, for the benefit of those who have already seen the light and whose chief concern in the early stages is to allay parental anxiety. The subsequent correspondence confirms my statement that the majority of dermatologists in this country agree with the views I expressed and it is reassuring to learn that both general and plastic surgeons are following the same policy.

With regard to nomenclature I claim neither originality nor authority but merely tried to define the terms used.

The point raised by Mr. Denis Browne as to whether really early treatment of small lesions is justifiable or not can only be decided by investigations, such as I and others have been attempting in the past thirty years, and it is disappointing that Mr. Browne can deduce so little evidence in favour of his very definite opinion in favour of treatment.

The only evidence I can offer is that out of 25 lesions of more than 3 cm. diameter 11 (44%) had disappeared without trace at 5 years and the others were all resolving satisfactorily; moreover in only 10 of these 25 cases had the lesion grown rapidly, i.e., faster than the child. Like Dr. Dowling, I have never seen a really large hæmangioma arise from a tiny spot. On the other hand, last year I saw an infant with over 100 small dermal lesions, of which none grew as large as 1 cm. in diameter and all showed signs of resolution by the 6th month.

Surely a few years' maternal embarrassment is of less importance than the patient's cosmetic appearance in adult life.

Exeter. J. R. SIMPSON.

KURU AND SPORADIC TREMOR SYNDROMES IN NEW GUINEA

SIR,—Wilson et al.[1] reported 24 cases of various tremor syndromes found sporadically in a population of about 100,000 natives in the Western Highlands of New Guinea and they have described 3 of these cases as examples of a kuru-like syndrome. They believe that " the implications of these newly discovered neurological disorders for the kuru problem are great ". In fact, they go on to say, " If the genetic hypotheses are correct, Melanesian natives may possibly have an unstable locus in their chromosomes at which mutation to produce inborn defects of metabolism leading to cerebellar, basal-ganglionic, and generalised central-nervous-system diseases of the kuru type is likelier than among other races." Later on, after making what appears to be a contrary suggestion that " a single kuru mutation might be assumed to underlie both syndromes ", they say " the ethno-environmental variables which determine altered clinical and epidemiological expression must be elucidated ". I think it needs to be made clear that no supporting evidence for these various genetic ideas has been put forward.

No genetic investigation has been described for these sporadic tremor syndromes. And there is no justification for assuming that the genetic hypothesis which has been put forward and found to hold for kuru [2–4] should also be charged with accounting for these different rare tremor syndromes found in another part of the island. Some of these disorders may indeed have a genetic basis but this awaits demonstration. It is unlikely that a genetic study could be made quickly, for the mere accumulation of genetic data for such sporadic disorders would probably be a very slow business. But even if some of these syndromes should be shown to have a genetic basis and this did depend, in fact, on a single locus, this would provide no support for the view that an " unstable locus " is involved. Furthermore, one can entertain such a suggestion only by ignoring the distinctive and significant family patterns in respect of kuru which have been found throughout the region concerned.[2–4] A high mutation rate at the kuru locus would not help to explain the astonishingly high frequency of kuru in the Fore population of the Eastern Highlands—surely the most puzzling and significant feature of the whole kuru population problem.

The population genetics situation presented by kuru may be unique, but our understanding of this tragic situation will not be advanced by confusing this uniqueness with a high degree of improbability for a genetical cause for which there is no evidence. In contrast with the suggestion made by Wilson et al. that these new syndromes may be " clinical variants of kuru and related to it in pathogenesis ", may I express the hope that further work will enable those workers to make a clear distinction between these sporadic syndromes and kuru—as indeed they are already distinguished in a number of important ways.

Department of Genetics, University of Adelaide. J. H. BENNETT.

MEDICAL NEEDS OF INDIA

SIR,—Your interesting and sympathetic leader last week refers to the scheme of postgraduate training " going back to a committee formed in 1941 under the chairmanship of the late Sir Bennett Hance ".

The Commission of Inquiry into Future Health Needs of India was in fact presided over by the distinguished Indian statesman, Sir Joseph Bhore. The Bhore Commission was composed of individuals drawn from many walks of life—political, financial, sociological, and medical—and obtained evidence from an impressive array of witnesses from India and oversea, including an advisory body from England under the late John Ryle, with Janet Vaughan and Weldon Dalrymple-Champneys, Professor Ognev from Moscow, and others from America and Australasia.

The Bhore report is a classic in the assessment of medical needs of an underdeveloped country.

London, S.W.1. GEORGE R. MCROBERT.

NEW WORDS REQUIRED

SIR,—In response to Mr. Caplan's request (Oct. 31), I suggest he may wish to consider a variation on the root word *errare*, to wander.

In current usage, aberrations are " slight deviations from the normal course " to navigators, while to astronomers an aberration is " a slight apparent shifting in position of a heavenly body ", so the root word " aberrant " seems to be a natural choice for Mr. Caplan's purpose.

My suggestion is the neologism " aberract " to denote a variation from optimum conduct.

Physical Restoration Division, Department of Public Health, Regina, Saskatchewan. D. F. CLARK Administrative Director.

1. Wilson, K., Zigas, V., Gajdusek, D. C. *Lancet*, 1959, ii, 699.
2. Bennett, J. H., Rhodes, F. A., Robson, H. N. *Aust. Ann. Med.* 1958, 7, 269.
3. Bennett, J. H., Rhodes, F. A., Robson, H. N. *Amer. J. hum. Genet.* 1959, 11, 169.
4. Bennett, J. H., Gray, A. J., Auricht, C. O. *Med. J. Aust.* 1959, ii, 505.

Parliament

Population (Statistics) Bill [1]

Dr. EDITH SUMMERSKILL regretted that in introducing this Bill to the Commons on Feb. 1 Miss EDITH PITT, parliamentary secretary to the Ministry of Health, had not explained more frankly the reasons why powers were sought to obtain further information about stillbirth and fœtal abnormalities, the age of fathers, and the duration of pregnancy. Dr. Summerskill thought that the information asked for in the schedule made it clear that the Bill was related to the genetic effect of nuclear radiation. The Minister had never been persuaded to admit that the increase in congenital abnormalities and in the incidence of leukæmia might be partially due to radioactivity. Yet here they had a Bill the import of which every scientist would know precisely, and an opening speech which had not for one moment touched on the real reason for its introduction.

Mr. DEREK WALKER-SMITH agreed that part of the object of the Bill was to find out more about the incidence of congenital abnormalities. They were acting on the advice of the Medical Research Council. Even if the number of mutational births was very small indeed, nevertheless there was something here which we had to study. The Medical Research Council was anxious to study it, and the Government were anxious to give the Council the facilities and scope under this Bill which would enable it do so.

QUESTION TIME

Preludin (Phenmetrazine)

Dr. EDITH SUMMERSKILL asked the Minister of Health whether he now proposed to prohibit the sale, without medical prescription, of 'Preludin'.—Mr. WALKER-SMITH replied: The Home Secretary, as an interim and urgent measure, has asked the Poisons Board to advise him which of the substances referred to by the Interdepartmental Committee should be limited to supply on prescription, under the Pharmacy and Poisons Act, 1933. The Poisons Board has held a meeting to consider the matter and he expects its report very shortly. Dr. SUMMERSKILL: May I remind the Minister that the whole question of the administration and consumption of this dangerous drug, preludin, was considered in this House a year ago after comments had been made in a coroner's court? Since then, there have been other fatalities. Could he not at least prohibit the sale of this drug without medical prescription? Will he read the report on the drug industry by a subcommittee of the Senate in the United States? In view of the fact that American firms are making such headway in this country, should we not take warning from the revelations which were made to the Senate last week?—Mr. WALKER-SMITH: The question of this drug can be dealt with only under the procedure of the Pharmacy and Poisons Act, 1933. An interim report by the Interdepartmental Committee was received on Jan. 21; the Poisons Board has already met, and the Home Secretary will be very shortly making his statement in regard to action.

Working Party on Legislation on Medicines

Mr. GRESHAM COOKE asked the Minister if he would give particulars about the Interdepartmental Working Party which he had set up on legislation concerning medicines.—Mr. WALKER-SMITH replied: This Working Party has been set up by the Secretary of State for Scotland and myself, in consultation with the Home Secretary, with the following terms of reference:

"to review the legislative provisions which relate to the control of medicinal substances and to recommend what changes should be made to rationalise and simplify the law with a view to ultimate amendment and consolidation."

It consists of 12 officials from the Government departments mainly concerned, of whom 2 have medical, 3 legal, and 2 pharmaceutical qualifications, and it will receive evidence from the organisations that are expert in this field.

1. See *Lancet*, 1959, ii, 976.

Hostels for Mental Patients

Mr. N. N. DODDS asked the Minister what progress was being made in providing hostels for people now confined in mental hospitals solely because there was no other provision for their welfare, in view of the desirability of enabling them to regain their liberty and self-respect as members of the community.—Mr. WALKER-SMITH replied: Local authorities have made a start in providing hostels of various kinds for the mentally disordered. It is likely that the main effect at first will be to avoid hospital admission for those not in need of it rather than to enable hospitals to discharge patients; local authorities and hospital authorities have, however, been asked to consult together in assessing future needs for the provision of hostels.

Poliomyelitis and Infective Hepatitis

Mr. L. A. PAVITT asked the Minister of Health what was his department's policy regarding the treatment of poliomyelitis and infective hepatitis in open wards. Mr. DEREK WALKER-SMITH replied: I have conveyed to hospital authorities the view that patients with any infectious disease should normally be nursed in isolation and recommended certain precautions to be observed when it is necessary to nurse such patients in open wards. I have suggested that special hospital units should be provided where practicable for the treatment of poliomyelitis.

University Places

Mr. MALCOLM MACPHERSON asked the Chancellor of the Exchequer, with reference to his announcement on Feb. 20, 1958, of a building programme for the universities for 1960–63, related to an estimated rise of student numbers to 124,000 in the mid-1960s, with the possibility of a further increase of 10% in the second half of the decade, whether he would not consult with the University Grants Committee as to the desirability of relating the building programme to higher numbers than these.—Mr. HEATHCOAT AMORY replied: The University Grants Committee last year made a full examination of this question in the light of the latest estimates of future numbers of seventeen and eighteen-year-olds in the schools and of other relevant factors. As a result they recommended strongly to me that they should be authorised to discuss with the universities an expansion of their capacity beyond the figure of 135,000 places which had already been agreed. They proposed to explore the possibility of providing an additional 35,000 to 40,000 by the late 1960s or early 1970s and to etsimate the capital cost involved. I have authorised this action and I understand that discussions with the universities have already begun.

Approved School Inquiry

In a statement on the recent report on the disturbances at an approved school, Mr. R. A. BUTLER, the Home Secretary, said that it included some general recommendations not requiring legislation. With these he was broadly in agreement, especially on the need for securing an adequate number of trained housemasters, and for pressing forward with plans for modernising and improving accommodation. He agreed also with the view that a limited provision of secure facilities was necessary to deal with the minority of difficult and troublesome boys with a disruptive influence on normal training.

The proposals involving legislation presented greater difficulty, and needed consideration in relation both to the legislation about the treatment of young offenders, which was foreshadowed in the Gracious Speech, and to the wider questions affecting approved schools. The Ingleby Committee had also under consideration some aspects of these questions. He would therefore prefer to defer further comment on the proposals for amending legislation until he had considered them in relation to his suggestions in the whitepaper. He was sure that the House would wish him to make comprehensive proposals for the treatment of young offenders, even if this involved some delay in introducing the Bill which was being prepared.

Obituary

WU LIEN-TEH

M.A., M.D. Cantab., LL.D.

PHYSICIAN to the Emperor and successive Presidents of China, director of the Manchurian plague prevention service, and director of the Chinese National Quarantine Service are unusual appointments for a Cambridge graduate to hold; but Dr. Wu was an unusual man. Fifty years ago, by his dramatic conquest of an outbreak of pneumonic plague in Northern Asia, he won an international reputation; he retained and enhanced it by his later work as a scientist, administrator, and writer.

He was born in 1879 in Penang where his father was a goldsmith. As one of a family of eleven children he had to make his own way in the world, but he won a Queen's scholarship, open to all the Straits Settlement, and he entered Emmanuel College, Cambridge, in 1894. At Cambridge, and indeed until he moved to China, he used the Cantonese-Malayan form of his name and was known as Gnoh Lean-Tuck. He took a first-class in the natural sciences tripos and in 1902 qualified from St. Mary's Hospital. With a research studentship from his own college he continued his bacteriological studies at the Liverpool School of Tropical Medicine, the Pasteur Institute in Paris, Halle University, and the Selangor Institute at Kuala Lumpur. In 1904 he returned to Penang and spent three years in general practice.

In 1907 he was invited to join the Chinese Government service at Tientsin and in 1908 he became vice-director of the Army Medical College. In 1910 he was sent by the Manchu Imperial Government to Harben to try to suppress a virulent epidemic of pneumonic plague that was killing over 100 people a day. He was given a dangerous and desperate task; for he had to organise plague hospitals and a plague service out of nothing.

In his autobiography, *Plague Fighter*, which appeared last year, he has described the desolate scene: the ground was covered with snow as far as he could see, and dotted here and there were groups of destitute refugees coughing and spitting blood—candidates for certain death. Wu had no protection, not even a mask, and his associates had no idea of the dangers of droplet infection. They stood before the unfortunate victims, huddled into corners, and breathed in their breath. Small wonder that nearly half the doctors and nurses died. It was impossible to bury the dead, for the ground was frozen iron-hard. Instead, they had to build high funeral piles and burn the corpses soaked in paraffin.

By organising medical assistants, nurses, and orderlies, by separating contacts, by isolating the sick, and by fumigating the homes Wu succeeded in three months in controlling the outbreak. He also succeeded, as he reported at the International Congress on Plague over which he presided at Mukden in 1911, in tracing the infection to the marmot hunters—poor men who hunted the giant marmot (or tarabagan) and caught the infection from the pelts hanging in their miserable huts. The tarabagan and the allied species of suslik were recognised as reservoirs of plague in the steppes and deserts of Manchuria and Siberia.

In 1912 the Manchurian Plague Service was set up and inevitably Wu became its first director. The Government allocated large sums for plague hospitals and the service became in effect a pioneer public-health service. Wu's classical treatise on *Pneumonic Plague* was published in 1926. In 1930, when the National Government established a quarantine service, Dr. Wu became director and equipped quarantine stations along the Chinese coast and at all important ports. He retired in 1937 to Ipoh, where he had begun his medical work; and there he continued in practice throughout his alert and active retirement. He died on Jan. 21.

During his varied life Wu received varied honours. He was a mandarin of the second rank and an honorary graduate of Johns Hopkins University. He had been decorated by the Czar of Russia and the President of France. He sat on many advisory committees of the League of Nations and he was a founder of the Chinese Medical Association. Of this versatile man P. M.-B. writes:

"Whatever the politics or whatever the revolution in his country, Wu lived and worked through it all. He was a world authority on the opium trade, and he was interested in cholera, anthrax, narcotics, quarantine, and venereal diseases. He never stopped writing; he attended every available medical congress in every continent; and he was known to everyone. He never forgot his English friends, and he would turn up in London, now and then, to take up the threads, reminisce on his undergraduate days, and tell of his heroes, amongst whom he numbered Patrick Manson and Andrew Balfour. In his massive autobiography, which is full of stories of his adventures, he showed himself as the great family man, proud of his family, proud of his offspring, and always proud of his Western contacts and forgiving for the sins of his European friends."

SAMUEL RONALD SINCLAIR

M.B., B.Sc. Belf., F.R.C.S.E., D.O.M.S.

Mr. S. R. Sinclair, ophthalmic surgeon to the Royal Victoria Hospital, Belfast, died on Jan. 18, while on holiday in London. He was 47 years of age.

He was the youngest son of the late Mr. Samuel Sinclair, of Cadogan Park, Belfast, and was educated at the Royal Academical Institution and Campbell College, Belfast, where he played in the rugby XV and the cricket XI. He graduated B.SC. at Queen's University in 1933 and took his medical degrees three years later. He was a house-physician in St. Thomas's Hospital, London, before the war, and in 1939 he joined the R.A.M.C. and served in the Middle East as a specialist in ophthalmology with the rank of major. On his return he took the F.R.C.S.E. in 1947 and was appointed a consultant by the Northern Ireland Hospitals Authority. He was on the staff of the Royal Victoria Hospital (where he was honorary secretary of the medical staff committee), of the Ophthalmic Hospital, Belfast, and of other hospitals in the Province. At Queen's University he was a clinical lecturer in ophthalmology.

T. W. D. writes:

"Sam Sinclair was a scratch golfer who captained the University team in 1936 and won the Irish mixed foursomes championship in the same year. He was a member of the Royal Belfast and Royal County Down Clubs and of Strangford Lough Yacht Club. His skill, efficiency, equanimity, friendliness, his quiet manner, and sterling character endeared him to all of his colleagues, the nursing staff, and his patients in whom he took a deep personal interest."

Mr. Sinclair leaves a widow and three daughters.

EDWARD WEISS

M.D. Jefferson

Dr. Edward Weiss, professor of clinical medicine at Temple University School of Medicine, Philadelphia, has died at the age of 64. He was a founder and past president of the American Psychosomatic Society.

H. R. R., who in 1953 as a Fulbright scholar worked with Dr. Weiss in Philadelphia, writes:

"It was an inspiration to discuss with him any problem in psychosomatic medicine, for he had a profound knowledge of clinical medicine and dynamic psychiatry and a razor-like intelligence. He had a way of formulating his opinions, both verbally and in writing, so that they appeared on the surface disarmingly simple. In his most recent book, *Don't Worry About Your Heart*, which was meant for the intelligent lay public, this adroitness is beautifully brought out.

"Edward Weiss was highly cultivated, a superb host, and a most generous friend and colleague. Among the social organisa-

tions to which he gave his time and skill were the Family Society of Philadelphia and the Marriage Council of Philadelphia. He was an earnest Anglophile, and in one of my last conversations with him only last December he outlined his plan to return to England in the next year or so to explore and paint the Cotswolds."

Diary of the Week

FEB. 7 TO 13

Monday, 8th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Mr. N. W. Please: Elements of Statistical Methods.
GUY'S HOSPITAL MEDICAL SCHOOL, S.E.1
5.30 P.M. Prof. Russell Fraser: Hyperparathyroidism.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Queen's College, Dundee.) Dr. J. M. Dodd, Mr. K. Ferguson: Methods of Assay of Thyroid Stimulating Hormone and its Applications.

Tuesday, 9th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Experimental Medicine and Therapeutics.* Dr. A. G. Spencer, Dr. G. C. Kennedy, Dr. C. T. Dollery: Chlorothiazide.
7.30 P.M. *Psychiatry.* Dr. W. B. Scoville (Connecticut), Mr. G. C. Knight, Mr. W. S. Lewin, Dr. R. G. McInnes, Dr. J. S. I. Skottowe, Dr. P. Macdonald Tow, Dr. D. W. C. Northfield, Dr. J. A. N. Corsellis: Selective Neurosurgical Operations in Psychiatry with Special Reference to Orbital Undercutting.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. R. D. Harkness: Liver Regeneration.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. Mr. Keith Vartan: Implications of Blood Pressure on Pregnancy.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. C. D. Calnan: Allergy and Immunology with Reference to the Skin.
MANCHESTER MEDICAL SOCIETY
8 P.M. (Clinical Sciences Building, York Place, Manchester.) *Surgery.* Mr. F. S. A. Doran: Rupture in the Groin. Mr. W. J. Metcalfe: The Low Operation for Femoral Hernia.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Prof. G. H. Lathe: Metabolic Contribution to Disease of the Brain.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Prof. A. C. Lendrum: Photomicrography.

Wednesday, 10th

ROYAL SOCIETY OF MEDICINE
4.30 P.M. *Physical Medicine.* Dr. J. G. Parish, Dr. C. D. Calnan, Dr. J. S. Lawrence: Heritable Disorders of Connective Tissue.
8 P.M. *Proctology.* Mr. W. B. Gabriel, Mr. T. McW. Millar, Mr. W. H. Bond, Mr. Gordon Ramsay, Dr. Basil Morson: Squamous Cell Carcinoma of the Anus and Anal Canal.
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Prof. M. Rachmilewitz (Jerusalem): Liver and Vitamin B_{12} Metabolism.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Antibiotics and Fungous Infections.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Prof. A. L. Cochrane: Epidemiology of Coalworkers' Pneumoconiosis.
MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) *Pathology.* Dr. H. Lempert: Treatment Control and the Pathologist. (Presidential address.)
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Queen's College, Dundee.) Dr. P. B. Marshall: Value of Catechol Amine Assays—Adrenaline and Noradrenaline Metabolism.

Thursday, 11th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2.
5 P.M. Dr. B. L. Coley: Tumours of Cartilaginous Origin. (Moynihan lecture.)
UNIVERSITY COLLEGE, Gower Street, W.C.1
5 P.M. Dr. Elizabeth Work: Mucopeptides of Bacterial Cell Walls. (Second of two lectures.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. A. T. James: Factors Affecting Blood Lipid Composition.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. S. C. Gold: Non-tuberculous Granulomas.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Dr. I. Doniach: Diseases of the Thyroid Gland.
ALFRED ADLER MEDICAL SOCIETY
8 P.M. (1, Wimpole Street, W.1.) Dr. D. N. Parfitt: Reflections on Fear and Learning.
NORTH WESTERN THORACIC SOCIETY
5 P.M. (Clinical Sciences Building, Manchester.) Dr. Donald Longson: Steroid Therapy. Dr. M. O'Connor: Radiation Hazards and the Chest Physician. Dr. J. C. P. Weber: Long-term Chemotherapy in the Elderly.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Dr. Ian Gordon: Rheumatic Disease in the Elderly: Polymyalgia Rheumatica.

Friday, 12th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
5.30 P.M. Mr. William McKenzie: Use of Rosen's Approach in Diagnosis and Treatment.
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
4.30 P.M. Dr. G. Ettlinger: Recent Ablation Studies in the Monkey.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH, 8
3.30 P.M. Prof. L. N. Pyrah: Aspects of Renal Calculus.

Notes and News

WORLD HEALTH ORGANISATION

SPEAKING to the Executive Board on the malaria eradication campaign, Dr. M. G. Candau, director-general of the World Health Organisation, said: "we had no illusions that the campaign would be easy, but the problems are being solved and if eradication fails it will be not for technical reasons but because we have not got the money to carry it out."

According to information received by W.H.O. from Governments, of the 1,238 million people that lived in originally malarious areas of the world, 258 million had been freed from this menace by the end of last year. Another 641 million live in the 65 countries and territories where eradication programmes are in progress, and 95 million are in 33 countries and territories which have realistic plans for such programmes. The board was told that the problem of mosquitoes becoming resistant to residual insecticides has proved not to be insurmountable and affects only 30 million people or less than 5% of the total number in areas where eradication programmes are in progress.

Mr. M. Siegel informed the board that there was an estimated shortage of 1·3 million dollars to finance W.H.O.'s share of costs of malaria eradication for 1960 as at present planned, and that 6·4 million was needed to ensure continuation of the work in 1961, even at the slightly slower rate of progress that had been projected. He deplored a situation in which over 95% of the 11·6 million dollars received before the end of 1959 had come from one member Government—that of the United States. Among the other countries that had contributed, few were among the more economically developed, and some had the lowest per-capita incomes of the world. During the discussion the situation was improved by the announcement of a new contribution by the U.S.S.R. of 1 million roubles in services and supplies, and another of £15,000 by Australia. The Government of Norway intends to propose a contribution of 100,000 dollars to Parliament as soon as W.H.O can announce that a certain number of other member States will contribute sums of the same relative size. A contribution of 1 million German marks from the Government of West Germany is also foreseen; and on Jan. 26 the board learned that the Canadian Government is asking Parliament for a contribution of 100,000 dollars.

The United States has made the first donation (300,000 dollars) to W.H.O.'s Special Account for Community Water Supplies which was set up last year to give technical assistance to Governments.

W.H.O.'s intensified programme of medical research was commended by Prof. Lowell T. Coggeshall (University of Chicago) as "intelligent" and practical. It will give high priority to services to research—e.g., the standardisation of nomenclature, techniques, and equipment; the establishment of reference centres for the identification of microorganisms, tissues, parasites, &c.; and the improvement of communications among research-workers and of their training. Next in priority will come demographic studies of the prevalence of diseases, and international coordinated research projects that may have a bearing on major W.H.O. programmes.

The hope was expressed that such research will tie nations together, establishing official contacts between research units that formerly only individuals achieved. This is already being done by bilateral agreements, Dr. Candau told the board, citing the agreement between the U.S.S.R. and the U.S.A. providing for, in part, exchanges of experience in the field of health and medical science.[1] Dr. Candau hoped that this move will lead to worldwide cooperation on a similar level, both Governments using W.H.O. to bring other countries into the sphere of their cooperative efforts. Prof. V. M. Zhdanov (U.S.S.R.) said that scientific institutions all over the world must further W.H.O.'s research programme. He predicted that in time it will become one of the most important activities of the Organisation.

1. See *Lancet*, Jan. 23, 1960, p. 233.

The Government of India has invited W.H.O. to hold the Fourteenth World Health Assembly in New Delhi in 1961. Though the Assembly usually meets in May, this meeting will probably take place in February, when the Delhi climate will be more propitious.

COST OF PHARMACEUTICAL SERVICES

IN his review of the Appropriation Accounts for 1958–59 [1] the Comptroller and Auditor General notes that the continuous increase in the cost of the pharmaceutical services of the National Health Service persisted during 1958. Though the number of prescriptions dispensed fell from 228 million in 1957 to 224 million in 1958, their total cost rose from £68 million to £73 million and the average cost per prescripton from 5*s*. 11½*d*. to 6*s*. 6½*d*. A growing proportion of these prescriptions were proprietary preparations (51% in 1958, as against 47% in 1957 and 37% in 1955). Proprietary preparations also accounted for a growing proportion of the cost of ingredients (72% in 1958, 70% in 1957, and 65% in 1955). Most of them, according to the classification of the Cohen Committee, are not therapeutically superior to standard preparations.

As their estimated cost to the N.H.S. was £30 million in 1958–59 (as against £20 million in 1955–56) the Comptroller, not unnaturally, was interested to have news of the voluntary price regulation scheme introduced in June, 1957, for a trial period of three years. The Ministry of Health had estimated that the scheme would save the Exchequer up to £750,000 on an annual expenditure of £20 million. In fact, on an annual expenditure of £28 million the scheme had only saved £412,000. One of the chief reasons for this was that ten drugs which had been expected to show price reductions of 25%–40% had in fact qualified for the export price criterion and no reduction had been obtained. According to the published accounts of 43 pharmaceutical firms for 1951–53 their percentages of profits had been above those of general industry and had lately tended to increase whereas the rate for general industry fell. The profit rates of the British subsidiaries of American concerns had consistently been much higher than those of general industry. The Comptroller freely admitted that these figures showed only very general trends and that many of the firms had important interests unconnected with the N.H.S. But he had noticed that a firm (whose profit in 1957 apparently exceeded 100%) in producing a proprietary drug on which the N.H.S. spent a large sum paid a substantial royalty on any crude material not bought from its American parent. The Comptroller was interested to note that more than half the N.H.S. expenditure on proprietary preparations was on the products of firms which achieved only 3·2% savings under the voluntary price regulation scheme. Because of the proportion of drugs excluded from price control and the industry's high rate of profits he doubts the efficacy of the scheme. The Ministry, however, believe that the scheme had imposed " some restraint on prices and led to some reductions ".

TRAINING IN GENERAL PRACTICE

AN experiment in training for general practice, financed partly by the Nuffield Provincial Hospitals Trust, is taking place in Winchester. A graduate intending to enter general practice holds a supernumerary appointment, paid at registrar rates, in hospital for one year, during which he obtains experience in various special departments according to his needs, including a six-month appointment in obstetrics and gynæcology, if he has not already held such a post. For the second year he is attached to a general practitioner, under the general-practitioner training scheme, to gain experience of aspects of medical practice other than his own. He is also introduced to the local-authority medical services. The object is to produce a general practitioner thoroughly versed in the many aspects of modern general practice, and to study methods of achieving this end.

The first appointment was made in Winchester last August and further appointments will shortly be made in Southampton and Portsmouth. Another hospital appointment will be available in Winchester in August, 1960, when the present holder moves into general practice under the scheme. An advertisement appears in this issue.

1. Civil Appropriation Accounts (Classes I-V), 1958-59. H.M. Stationery Office. 1960. Pp. 349. 19*s*.

LADY EWING MEMORIAL

THE work of the late Lady Ewing in the cause of the education of deaf children won worldwide renown, and the high reputation of the department of education of the deaf at Manchester University sprang largely from her remarkable skill as a teacher. Her friends and former students now feel that this recognition should take a more permanent form and that some suitable memorial to her life and work should be established. They believe that many people, especially those whom she helped directly and indirectly, would be glad to contribute to the cost of its foundation. It has accordingly been decided to establish a research scholarship to be known as the Irene Ewing Research Scholarship. Contributions should be addressed to Mr. F. W. Cockersole, 80, Wellington Road, Edgbaston, Birmingham, 15. Cheques should be made payable to the Lady Ewing Memorial Fund.

University of London

Dr. E. B. Chain, professor of biochemistry at the Istituto Superiore di Sanita, Rome, and scientific director of the International Research Centre and head of the biochemistry department, has been appointed to the university chair of biochemistry at the Imperial College of Science and Technology from Oct. 1, 1961. Professor Chain was awarded in 1945 a Nobel prize for medicine jointly with the late Sir Alexander Fleming and Sir Howard Florey for their work on penicillin.

The Isaac Wolfson Foundation has given the college £350,000 to build and equip laboratories for biochemistry and chemical microbiology in Professor Chain's department and for the support of teaching and research. The equipment of the Wolfson Laboratory will include fermentation units of comparatively large size and workshops for advanced mechanical and electronic equipment. It will provide accommodation for training and research in the borderland between biochemistry and chemical engineering, and for research on the biochemical production of chemicals.

Mr. Kenneth McLay has been appointed reader in otology at the Institute of Laryngology and Otology.

University of Edinburgh

Dr. E. S. Blackadder has been appointed part-time lecturer in the general-practice teaching unit and Dr. R. F. Robertson member of the clinical teaching staff in the department of medicine.

University of Birmingham

The following appointments have been made:

Sir Arthur Thomson, senior fellow in medical history; Dr. R. F. Fletcher, lecturer in the department of medicine; Dr. J. D. Blainey, part-time lecturer in the department of experimental pathology (metabolic diseases); Mr. J. A. Williams, lecturer in the department of surgery.

University of Exeter

On May 4 the honorary degree of LL.D. will be conferred on Dr. C. J. Fuller.

Royal College of Obstetricians and Gynæcologists

At the meeting of council on Jan. 30, with the president in the chair, the following candidates were elected to the membership:

Armaity Aspandiar Anklesaria, Alison M. Armstrong, M. P. Awon, Amarendra Banerjee, J. D. Begg, Kwesi Kobea Ogve Bentsi-Enchill, K. G. Bland, Kathleen A. S. Brosnan, G. R. Brown, Solomon Burgin, Biman Kumar Chakrabarti, Supriya Chakravorty, F. R. Clark, Harry Cohen, J. B. Comerford, F. G. Cox, Gerda J. Crow, M. M. De La Harpe, R. A. Don, Shelia L. B. Duncan, Solomon Ende, P. H. Foote, A. C. Fraser, K. E. Free, I. K. Furler, W. T. Gallagher, Susan George, Ronald Giles, C. S. Harison, P. D. Hill, Uriah Jacobson, Snehalata Bhujanga Kamath, Pun Shui Kan, Swadesh Kataria, Brendan Keane, Bhabesh Chandra Lahiri, Ariffin Bin Ngah Marzuki, Tanendra Nath Mitra, T. Khoon-Fong Ng, D. B. Paintin, Heather M. Panton, Mary C. W. Paterson, E. C. Pixley, G. L. S. Rankin, L. J. Schewitz, S. C. Simmons, Nargese Jehangir Talati, E. P. W. Tatford, Molly E. Towell, Mary M. Tyndall, R. J. Venn, N. F. Walker, W. A. W. Walters, D. K. Williams, L. H. Wright.

Royal College of Physicians of London

At the comitia on Jan. 28, with Sir Robert Platt, the president, in the chair, the following, having satisfied the censors' board, were elected to the membership:

G. M. Ardran, M.D. Lpool, John Bamforth, M.B. Cantab., M. A. Barraclough, M.B. Lond., J. R. Billinghurst, B.M. Oxon., E. J. M. Bowlby, M.D. Cantab., D. E. Christian, M.B. Lond., G. W. A. Dick, M.D. Edin., P. M. S. Gillam, M.B. Cantab., Maurice Gross, M.B. Lond., D. D. Guttman, B.M. Oxon., R. M. McCredie, M.B. Sydney, William MacKenzie, M.D. Lond., A. B. Myles, M.B. Cantab., K. A. K. North, M.B. N.Z., H. L. Nossel, M.B. Cape Town, E. D. O'Callaghan, M.B. Queensland, P. T. Pickens, B.M. Oxon., Mohamed Sadek Sabour, M.B. Ain Shams, N. L. Schwartz, M.B. W'srand, P. J. Scott, M.B. N.Z., R. S. J. Simpson, M.B. Queensland, J. H. Stewart, M.B. N.Z., Weland Dinnis Stone, B.M. Oxon., Vetherednam Thuraisingham, M.B. Malaya, W. E. Watson, M.B. Lond.

Licences to practise were conferred on the following candidates who had passed the final examination of the Conjoint Board:

J. H. Ainsworth, E. G. Anderson, R. B. Andrews, R. I. A. A. Aubee, J. K. Bandoh, Sheila A. Beningfield, C. A. C. Bennett, R. P. Bishop, P. G. H. J. Bosley, Margaret Bown, Isobel J. N. Bradbury, J. S. Brewer, M. G. Brook, Diana C. Brown, J. P. B. Budgen, R. G. Bury, Janet R. Carruthers, M. E. Carruthers, Francis Carter, Margaret E. Cash, Anne J. Cawthorne, M. J. Chamberlain, Glen Champion, M. J. S. Coe, Bertha C. A. Coker, T. J. Colbridge, G. P. Coleman, Heather J. Collins, D. H. Coombe, A. S. Cooper, Linda F. Courtier, C. S. D. Crane, T. W. Darling, Faram Dastur, H. R. Davies, J. G. Deller, E. R. Dixon, M. W. O. Dunwoody, Kathleen J. B. Edwards, Ekpo Ita Efiong, Mary Ellis, M. D. Farrar, J. T. L. C. Fernando, A. E. Finnigan, D. J. Fishlock, P. R. Goddard, A. B. Griffiths, J. B. Gritton, J. H. Hackwood, Edna Hallam, D. R. Harvey, I. B. Hayter, Ann Henley, Pauline B. Hird, K. E. F. Hobbs, R. C. Hodge, G. T. Hollingworth, A. S. Horner, Peter Howard, E. G. Hoyen-Chung, K. E. E. Hubble, M. K. G. Hudson, W. F. G. Hulley, M. J. Hunter, R.-K. R. Innes, Peter Jackson, C. W. Jamieson, Rosemary Khin Zaw, R. S. Kirk, Elizabeth S. Kitchin, C. C. Korvin, A. P. Lees, Eva Lester, Chooi Cheah Lim, J. D. Lloyd-Still, S. J. McDonald, Stuart McHardy-Young, Marion MacLellan, Margaret R. McMinn, Margaret M. McNamara, J. J. M. Marot, June E. Marrable, Harriet M. C. Mason, Pamela J. Massie, R. E. May, R. D. G. Milner, R. L. Mitchell, Michael Modell, M. A. Modelski, J. F. Moore, T. S. Morley, A. E. Morris, M. D. R. Morris, J. F. Murray, A. J. H. Nix, J. R. Norman, George Nuki, D. Ajuebitsi Ogbe, P. M. Olley, E. G. J. Olsen, S. M. Patient, H. G. Peters, J. B. Phillips, Douglas Pickering, C. I. Porter, A. R. C. Ralph, Durgapursad Ramprotal, L. M. Razavi, R. J. Rew, D. A. Reynolds, M. T. Reynolds, Janet Riddle, A. D. Rogers, P. J. Y. Scott, Paul Sharpstone, C. M. Signy, G. M. Slade, J. K. Smallshaw, M. J. Smith, Akanni Olufemi Olakunle Sorungbe, F. B. Stephenson, Mary Stewart, A. E. Stocks, Norma A. Taylor, R. G. N. Thomson, Reginald Tiru-Chelvam, P. M. J. Tombleson, Madueke Ugwunze, Keith Urwin, P. L. H. Vernon, B. A. Waldron, Judith G. Walker, B. A. Wallace, P. J. Watt, Tessa Westcott, Myra Wharf, W. F. White, R. W. Wille, D. E. Williams, J. G. Williams, Norman Williamson, J. G. Wingfield, Manmohan Singh Wirk, J. D. Wonham, Adeline Chung Ling Yen.

The following diplomas and those mentioned in our issue of Jan. 23 (p. 234), were conferred jointly with the Royal College of Surgeons:

D.A.—George Chasapakis.
D.C.H.—Rabindra Nath Mukerjee.
D.I.H.—Fredoon Kaikhushro Amroliwalla, J. C. Cape, Jitendra Chandra Chakrabarti, Catherine J. S. Gauvain, P. A. Lee, Zivojin Lukic, I. A. McIntosh, Vlasta Mucic, J. H. Neal, Akhouri Ram Nandan Prasad, R. C. Robb, E. R. Simpson, Rosemary Trewby.
D.P.M.—A. K. M. N. Chowdbury.
D.T.M. & H.—T. W. Brown, D. H. Cook, Ahmad Hadjian, Tanvir Islam, Ashok Dwarkanath Laud, Lyn W. Padgett, Robert Scott, Vafiuddin Shaikh, G. R. Thompson.

Royal Society

At a meeting of this society to be held on Feb. 11 at 4.30 P.M. at Burlington House, Piccadilly, London, W.1, Dr. Elsie Widdowson, Prof. R. A. McCance, and Mr. J. W. T. Dickerson will read papers on some effects of accelerating growth.

Medical Research Council

Fellowships in Clinical Research.—The Council invite applications for a further series of fellowships in clinical research, tenable at centres in the United Kingdom during 1960–61. These fellowships are open to suitably qualified medical graduates who wish to prepare for a career in clinical research.

Further particulars and forms of application may be obtained from the secretary of the Council, 38 Old Queen Street, London, S.W.1, with whom applications must be lodged by March 15.

College of General Practitioners

Last April the North-West England faculty of the college held in Manchester a symposium on Coronary Disease in General Practice. Over 750 doctors applied to attend, and the success of the venture has decided the faculty to hold another similar symposium this year. It will be at the Midland Hotel, Manchester, on Sunday, April 10, with Lord Cohen of Birkenhead as chairman. This year's subject is Chronic Bronchitis in General Practice.

British Medical Association

Sir George Pickering has been nominated as president of the Association for the year 1963–64.

Imperial Cancer Research Fund

Lord Salisbury has succeeded the late Lord Halifax as president of this Fund.

Scientific Attaché in Soviet Russia

Dr. D. A. Senior, a senior principal scientific officer on the staff of the Department of Scientific and Industrial Research, has been appointed scientific attaché to the British Embassy in Moscow. His assignment covers the physical sciences, biology, medicine, and agriculture.

Glasgow Royal Mental Hospital

A two-storeyed extension to this hospital at Gartnavel has recently been completed. It has cost £100,000 and has 80 beds arranged in 32 single rooms and 8 six-bed dormitories. On each floor there is a day-room, a quiet room for reading and writing, and a dining-room. Treatment rooms, consulting-rooms, and a waiting-room for visitors are also included.

Nutrition and the Elderly

The Nutrition Society will hold a symposium on this subject at St. Bartholomew's Hospital Medical College, London, E.C.1, at 9.45 A.M. on Saturday, March 19. The speakers will include Prof. K. J. Franklin, Dr. C. A. Boucher, Dr. E. Woodford-Williams, Dr. Alex Comfort, Dr. B. E. C. Nordin, Dr. C. J. Earl, and Dr. J. V. G. A. Durnin. Further particulars may be had from Miss D. F. Hollingsworth, Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, S.W.1.

Training of Mental Health Staff

The Minister of Health has sought the advice of his Standing Mental Health Advisory Committee on the training required by the staff of centres provided by local health and hospital authorities for the occupation or training of mentally subnormal persons, and the Committee has appointed a subcommittee to consider this. The members include: Dr. J. A. Scott (chairman), Dr. D. H. H. Thomas, Dr. J. S. Hamilton. The secretary is Mr. A. G. Rose, Ministry of Health, Savile Row, London, W.1.

The Biochemical Society will hold a symposium on the biochemistry of mucopolysaccharides, on Saturday, Feb. 13, at 10 A.M., at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2.

Appointments

BOYD, MARY M. M., M.D. Edin., PH.D. Lond., M.SC. N.Z., M.R.C.P., D.C.H., D.P.H., D.OBST.: senior M.O. (maternal and child welfare), Cornwall.

FORREST, A. D., M.D. St. And., M.R.C.P., D.P.M.: consultant psychiatrist, Royal Edinburgh Hospital for Mental and Nervous Disorders.

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Births, Marriages, and Deaths

BIRTHS

GELLMAN.—On Jan. 22, at the Winnipeg General Hospital, to Dr. and Mrs. D. D. Gellman (formerly Dr. Vera Armett) of Ste. 307, 81, Roslyn Road, Winnipeg—a son, Andrew John.